# Drug Absorption and Bioavailability

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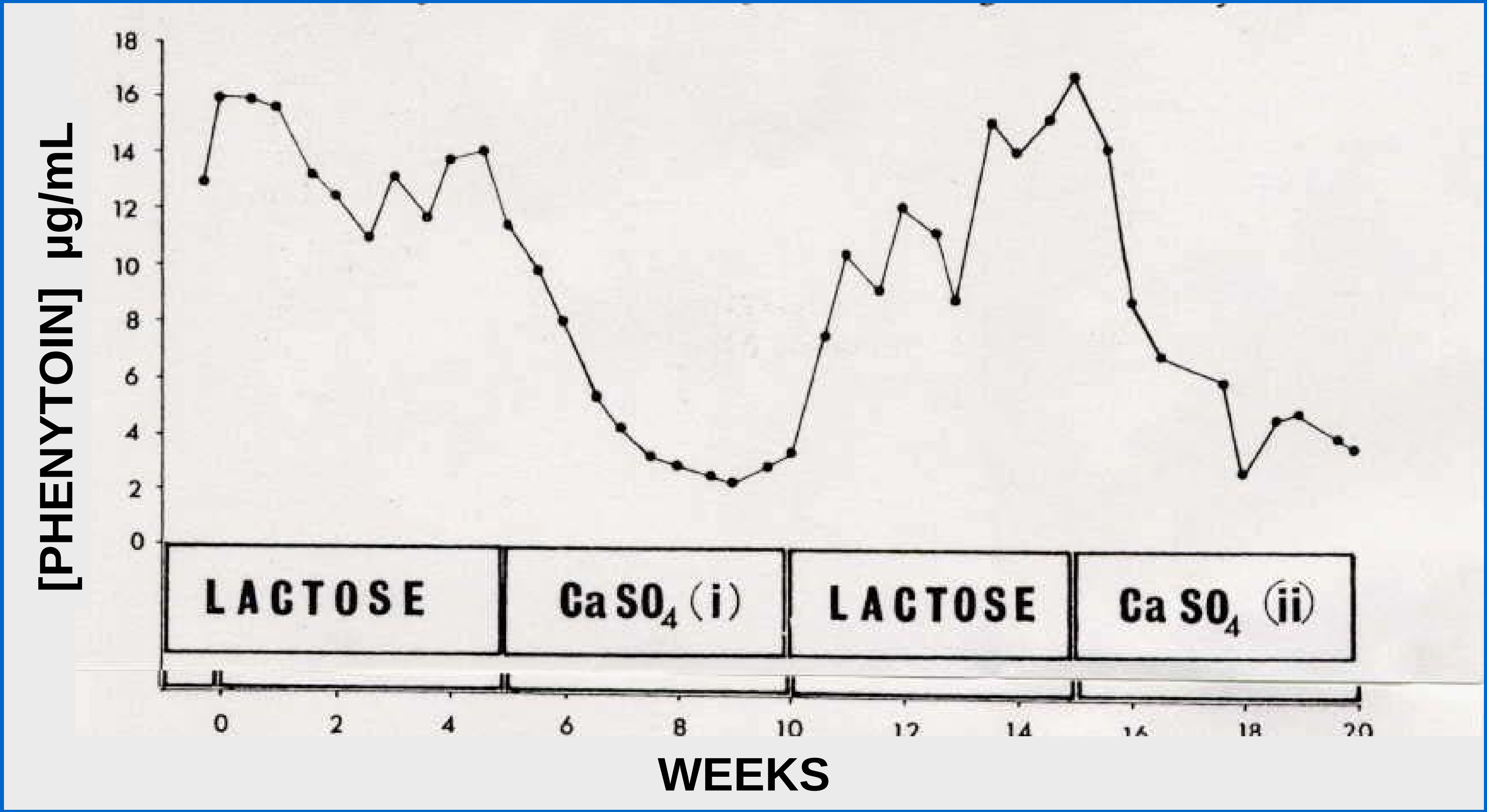
# GOALS of Drug Absorption and Bioavailability Lecture

- ***Factors* Affecting Drug Absorption**
- ***Estimation* of Bioavailability**
- ***Clinical Significance* of Differences in Bioavailability**
- ***Prediction* of Bioavailability in High-Throughput Drug Candidate *Screening***

# Factors Affecting DRUG ABSORPTION

- **Biopharmaceutic Factors**
  - Tablet compression
  - Coating and Matrix
  - Excipients
- **Interactions**
  - Food
  - Other Drugs
  - Bacteria
- **Physiological Factors**

# Change in PHENYTOIN *Excipients* Results in Epidemic Toxicity*

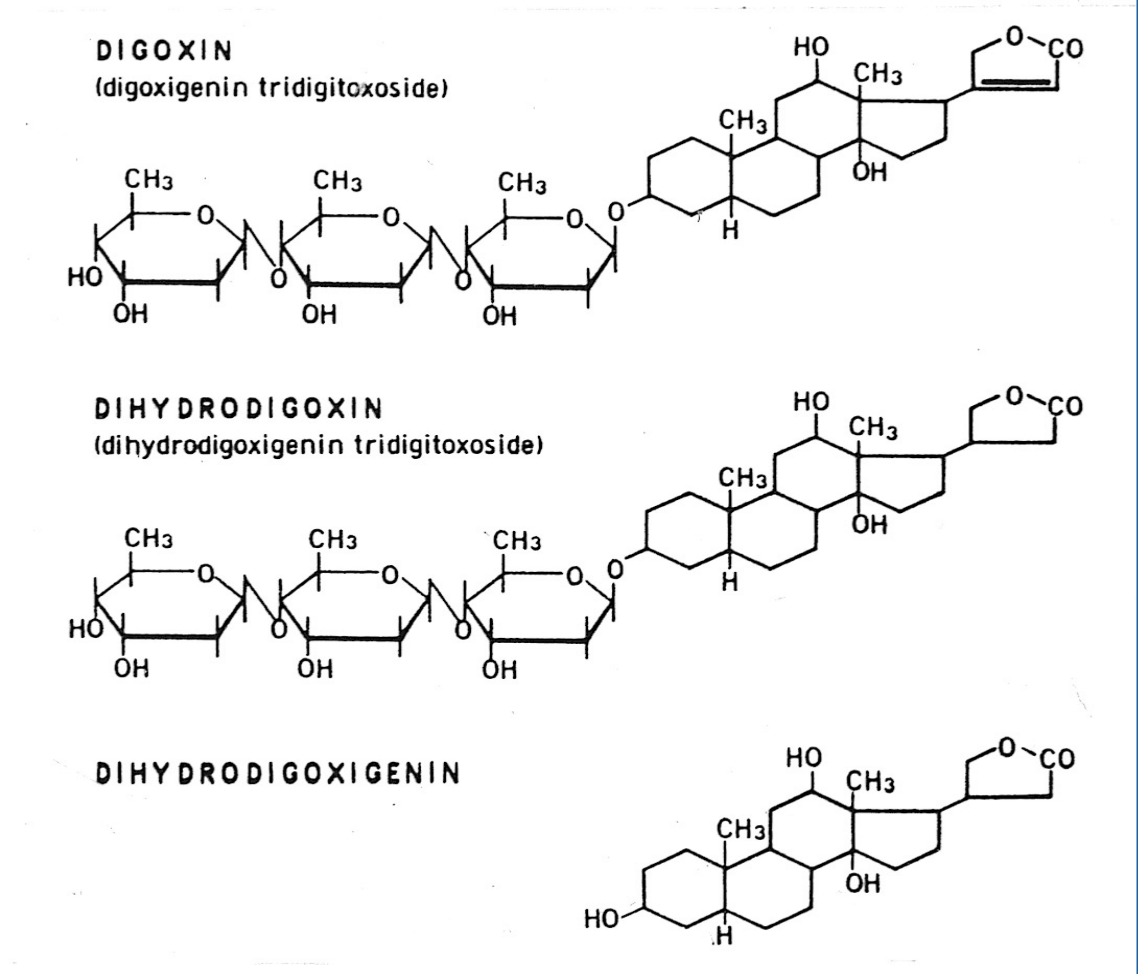



* Bochner F, et al. Proc Aust Assoc Neurol 1973;9:165-70

# Factors Affecting
# DRUG ABSORPTION

- Biopharmaceutic Factors
- **INTERACTIONS**
  - Food
  - Other Drugs
  - Bacteria
- Physiologic Factors

# *ENTERIC METABOLISM* OF DIGOXIN*




* Lindenbaum J, et al. N Engl J Med 1981;305:789-94.

# Factors Affecting DRUG ABSORPTION

- Biopharmaceutic Factors
- Interactions
- PHYSIOLOGICAL FACTORS

# Drug Absorption

Passive Non-Ionic Diffusion:

Primary mechanism for most drugs.

# Drug Absorption

## - Specialized Transport Mechanisms

**Large Neutral Amino Acid Transporter:**

***L-Dopa, Methyldopa, Baclofen***

# Drug Absorption

## - Specialized Transport Mechanisms

**Oligopeptide Transporter (PEPT-1):**

***Amino-beta-lactams***

***ACE Inhibitors***

# Drug Absorption

- Specialized Transport Mechanisms

**Monocarboxylic Acid Transporter:**

*Salicylic acid*

*Pravastatin*

# FALLACIES Concerning Gastric Drug Absorption

- Acidic Drugs absorbed in the stomach
- Basic Drugs absorbed in the small intestine
- Gastric pH is always acidic

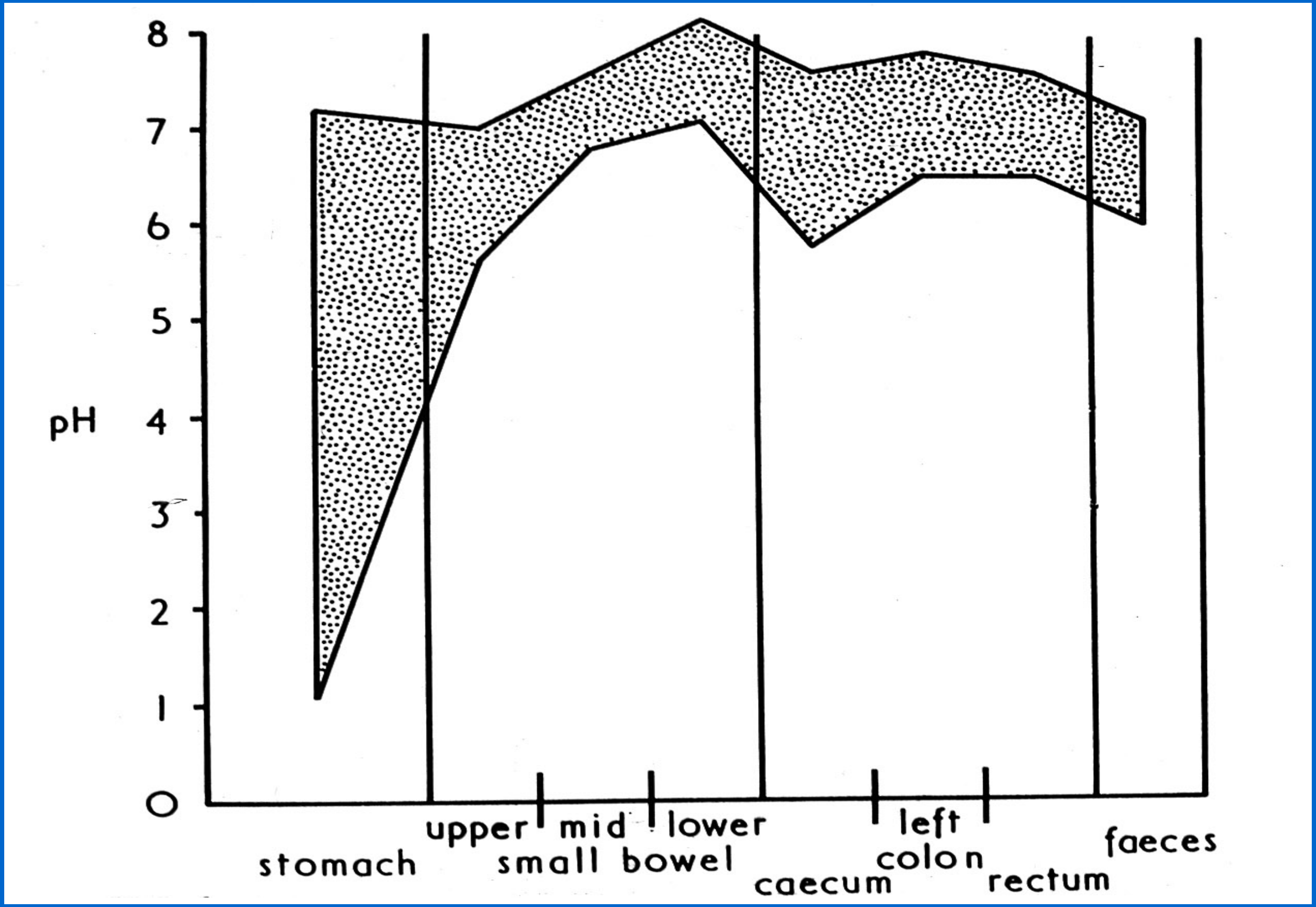
**In Fact, most drug absorption occurs in the SMALL INTESTINE**

# ASPIRIN ABSORPTION FROM *STOMACH AND SMALL INTESTINE**

| TABLE 1: ASPIRIN (ASA) ABSORPTION FROM SIMULTANEOUSLY PERFUSED STOMACH AND SMALL INTESTINE (3) | | | |
|---|---|---|---|
| pH | ASA ABSORPTION (micromol/100 mg protein/hr) | | ASA SERUM LEVEL (mg/100 ml) |
| | STOMACH | SMALL BOWEL | |
| 3.5 | 346 | 469 | 20.6 |
| 6.5 | 0 | 424 | 19.7 |

* From: Hollander D, et al. J Lab Clin Med 1981;98:591-8

# Variation in Gastric and Intestinal pH*




* Meldrum SJ, et al. Br Med J 1972;2:104-6.

# PHYSIOLOGICAL FACTORS
# Affecting Drug Absorption

- **Rate of gastric emptying** **is a major determinant of *initial delay* in drug absorption.**
- **Intestinal motility** **is a determinant of the *extent* of drug absorption.**

# *PATTERNS* OF GASTRIC MOTOR ACTIVITY

## FASTING *(Cyclical Pattern < 2 HR)*

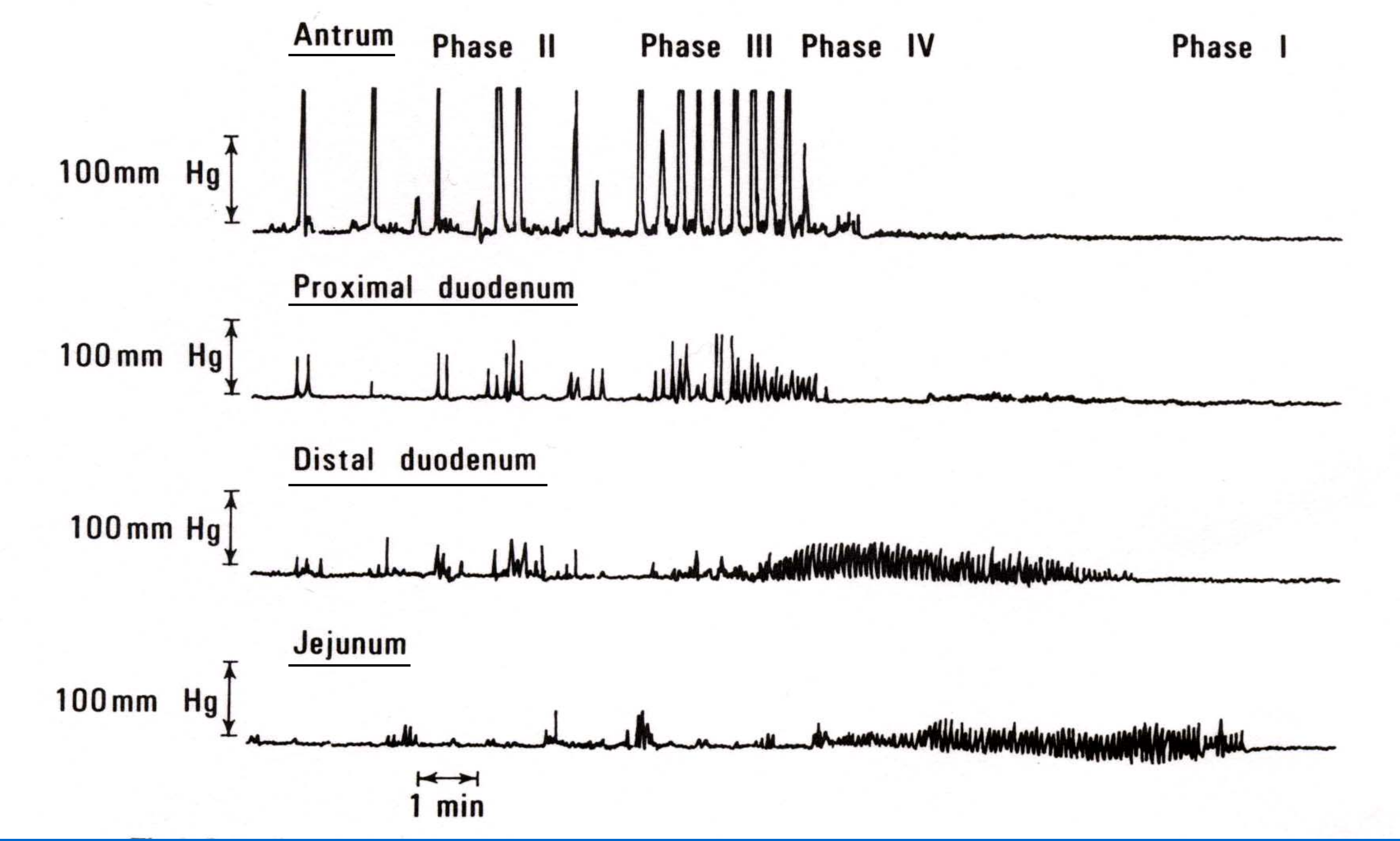
**Phase 1 - Quiescence**

**Phase 2 - Irregular Contractions**

**Phase 3 - Major Motor Complex Burst**

**Phase 4 - Transition Period**

# Interdigestive Intestinal Motor Activity in Humans*



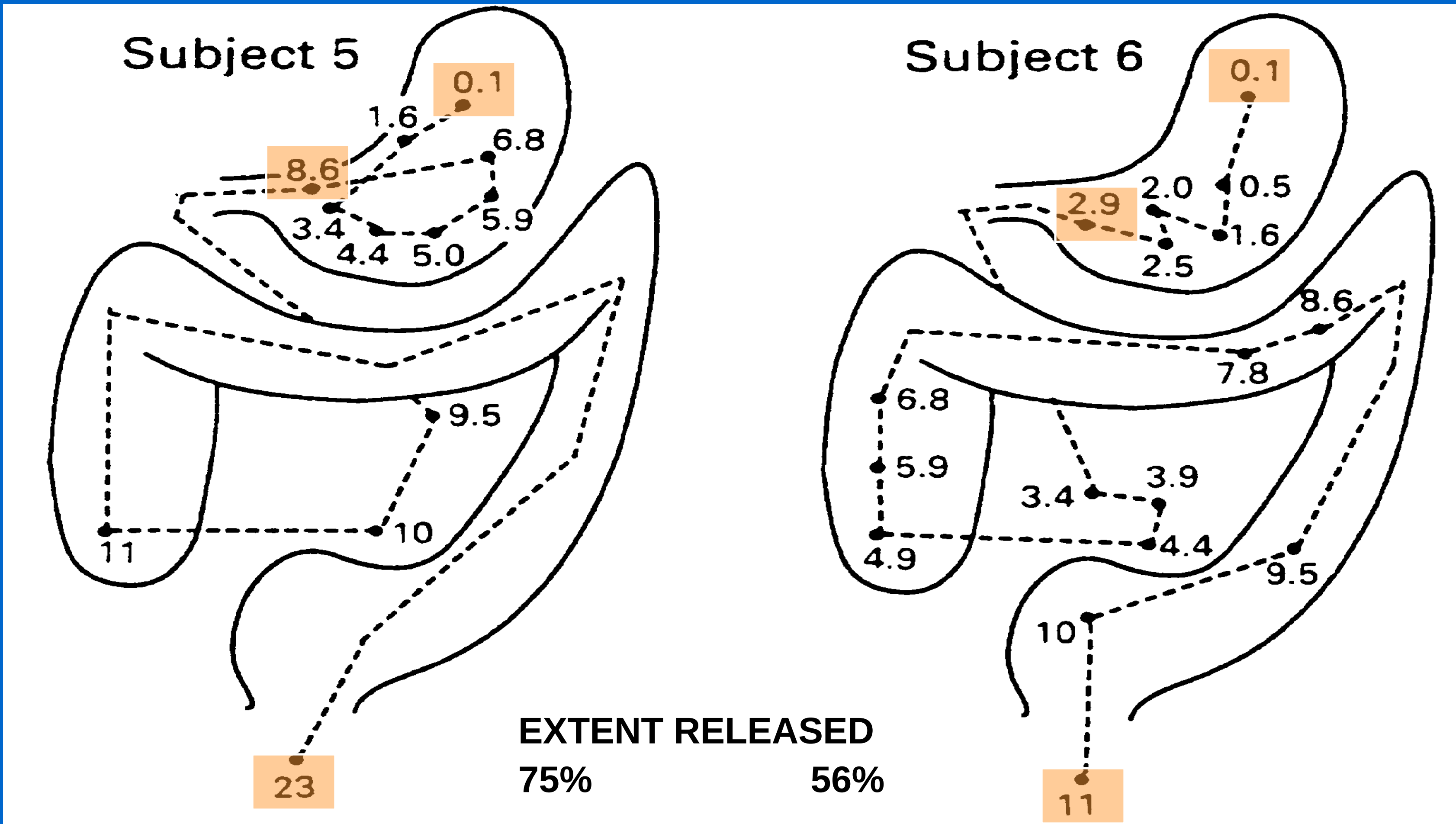

*From: Rees WDW, et al. Dig Dis Sci 1982;27:321-9.

# *PATTERNS* OF GASTRIC MOTOR ACTIVITY

**POST PRANDIAL (*Up to 10 hr delay*)**

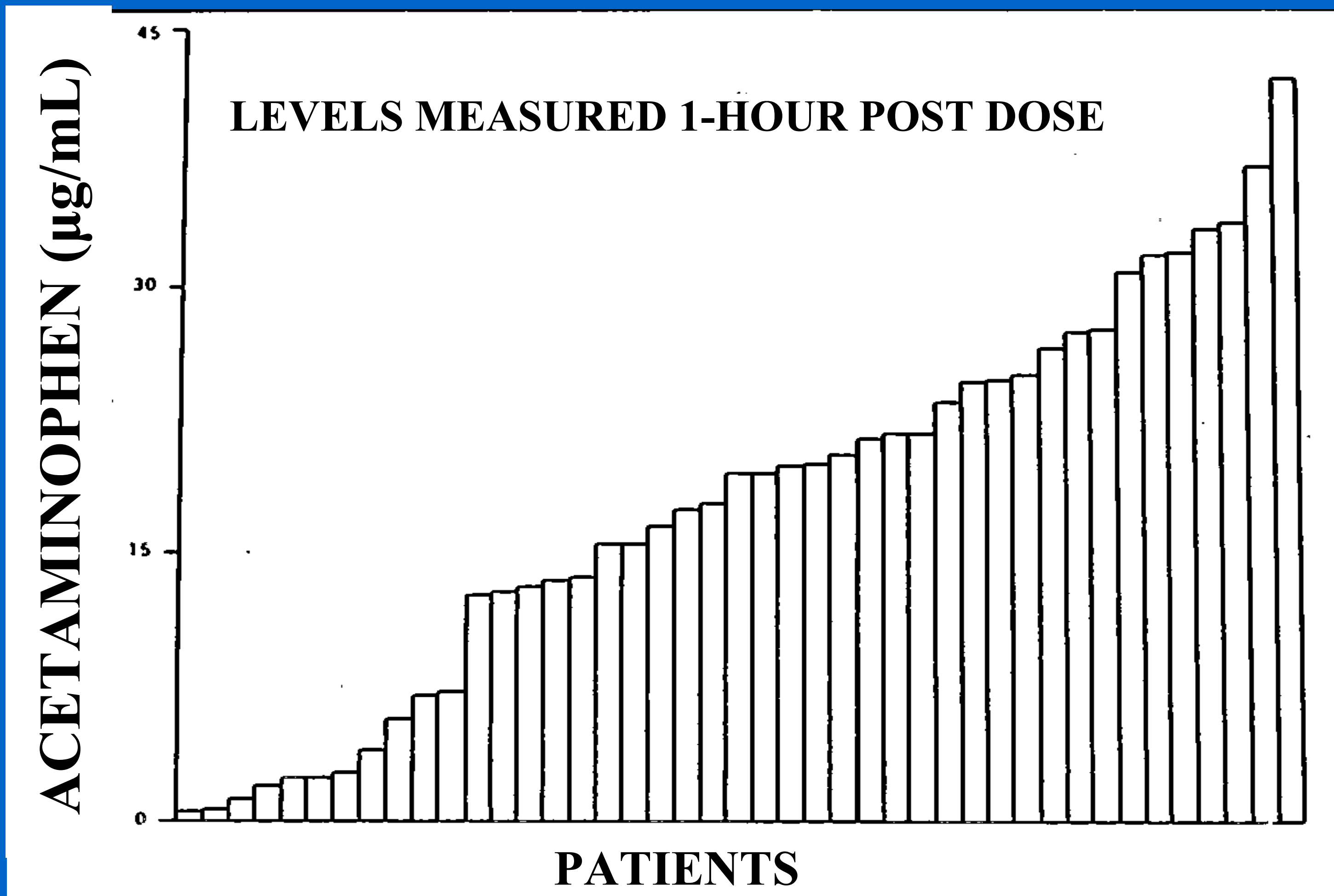
- **Pylorus constricted**
- **Antral contractions reduce particle size**

# *GI TRANSIT - SUSTAINED-RELEASE* **CARBAMAZEPINE** *FORMULATION**



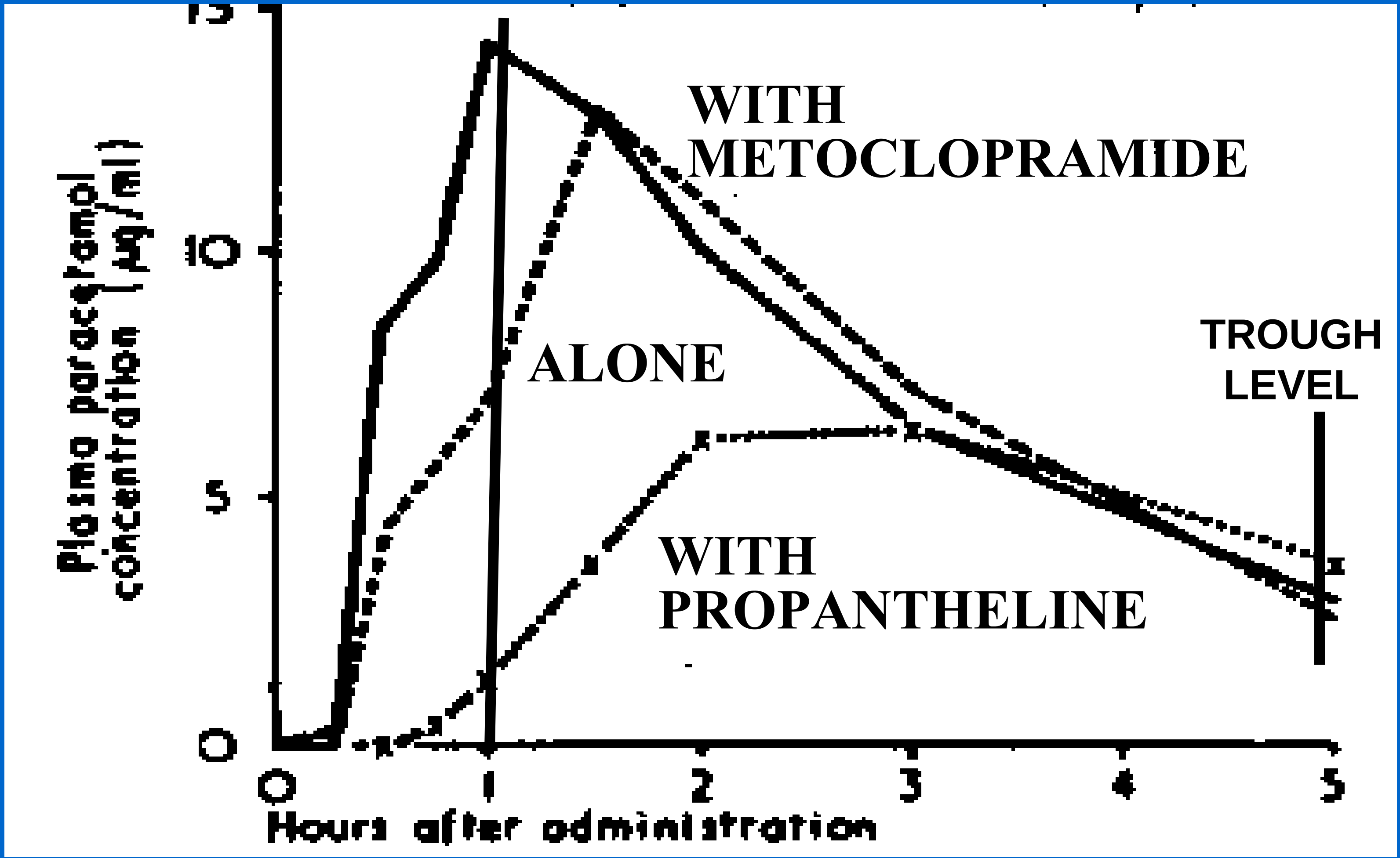

*From: Wilding IR, et al. Br J Clin Pharmacol 1991;32:573-9.

# Variation in “Peak” Levels
## ACETAMINOPHEN*



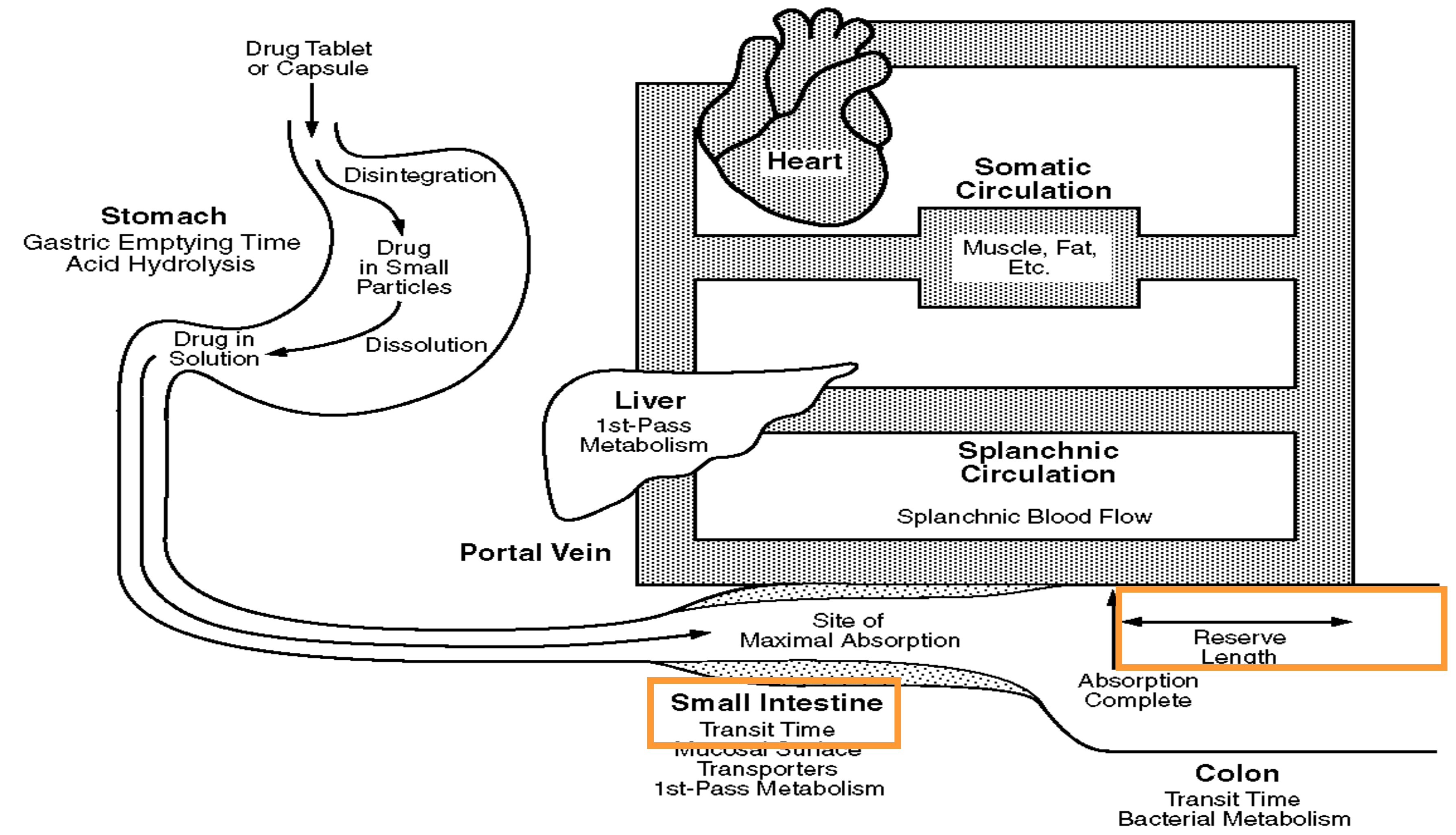

* Prescott LF. Med Clin N Am 1974;42:907-16.

# Gastric Emptying Rate Affects ACETAMINOPHEN Absorption*




*From: Nimmo J, et al. Br Med J 1973;1:587-9.

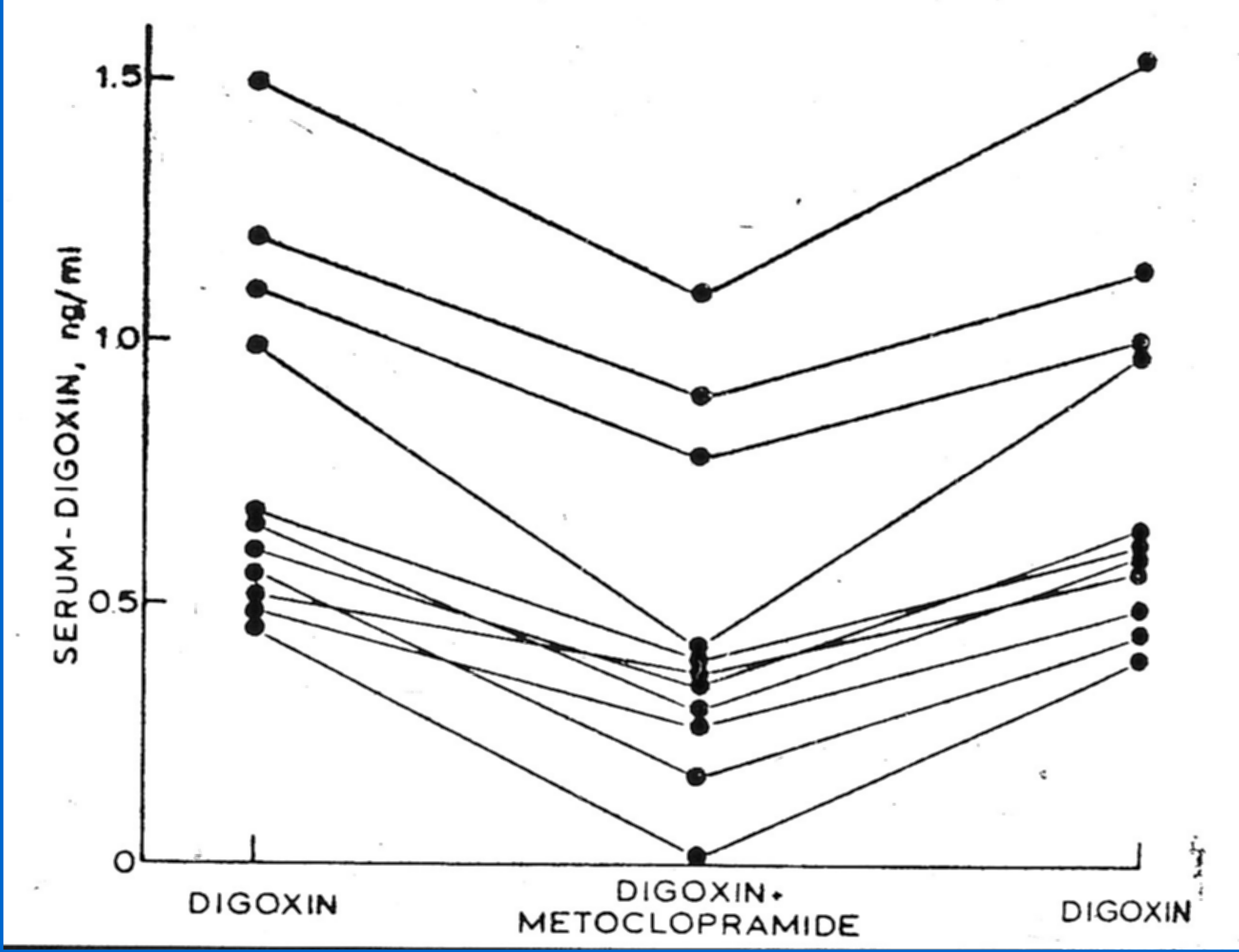
# Factors Affecting RATE and EXTENT of Drug Absorption



# RESERVE LENGTH

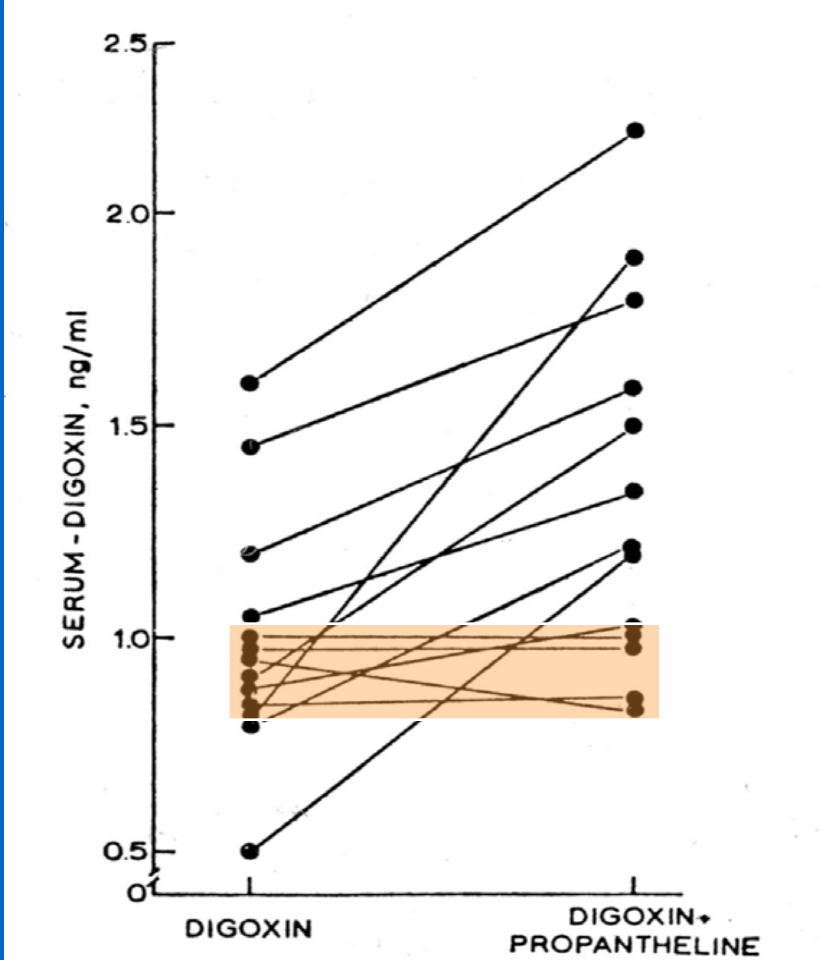
***RESERVE LENGTH*** **is the anatomical length over which absorption of a drug *can* occur *MINUS* the length at which absorption is complete.**

# Effect of METOCLOPRAMIDE on Digoxin Absorption*



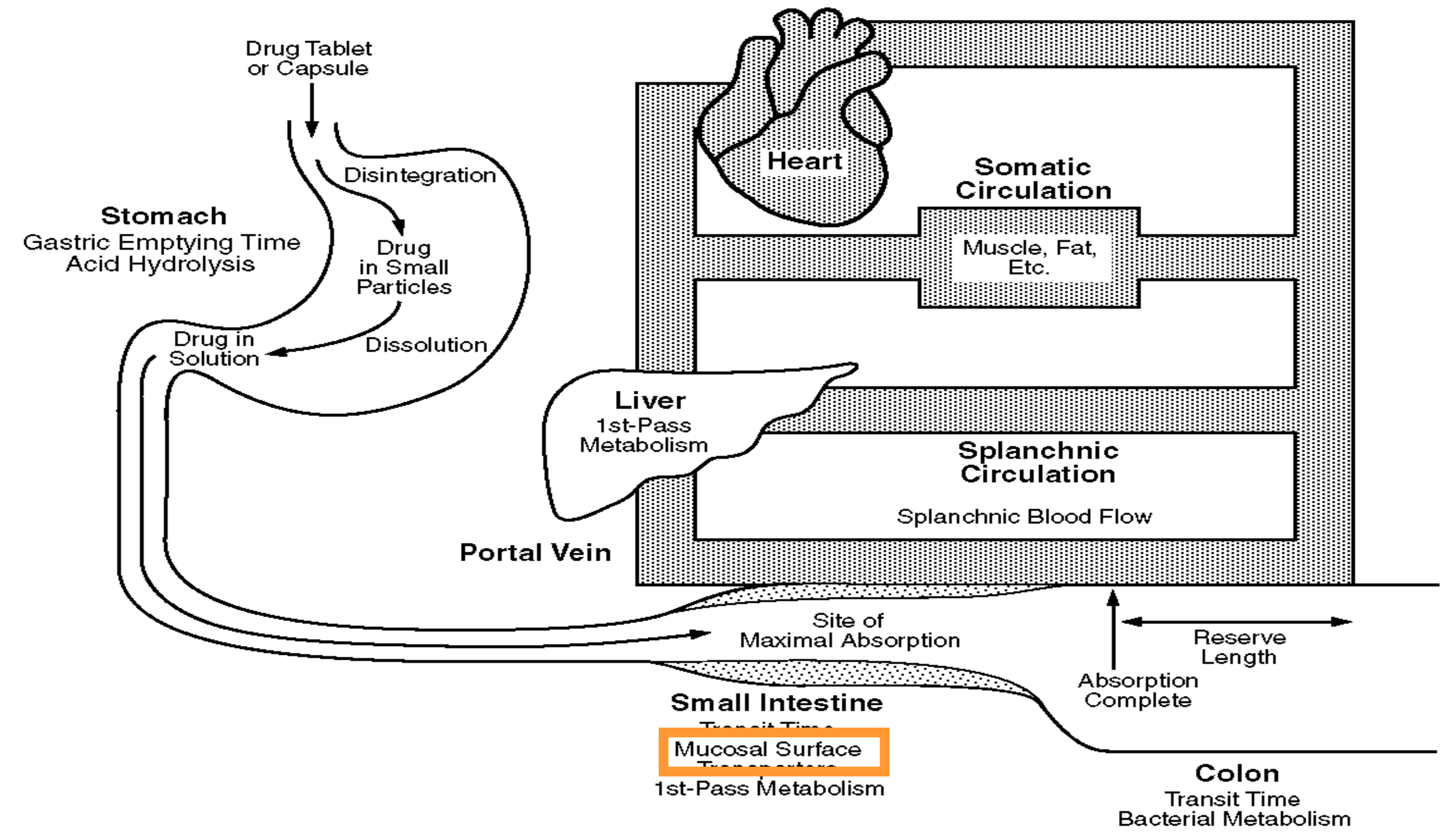

*From: Manninen V, et al. Lancet 1973;1:398-99.

# Effect of PROPANTHELINE on Digoxin Absorption*



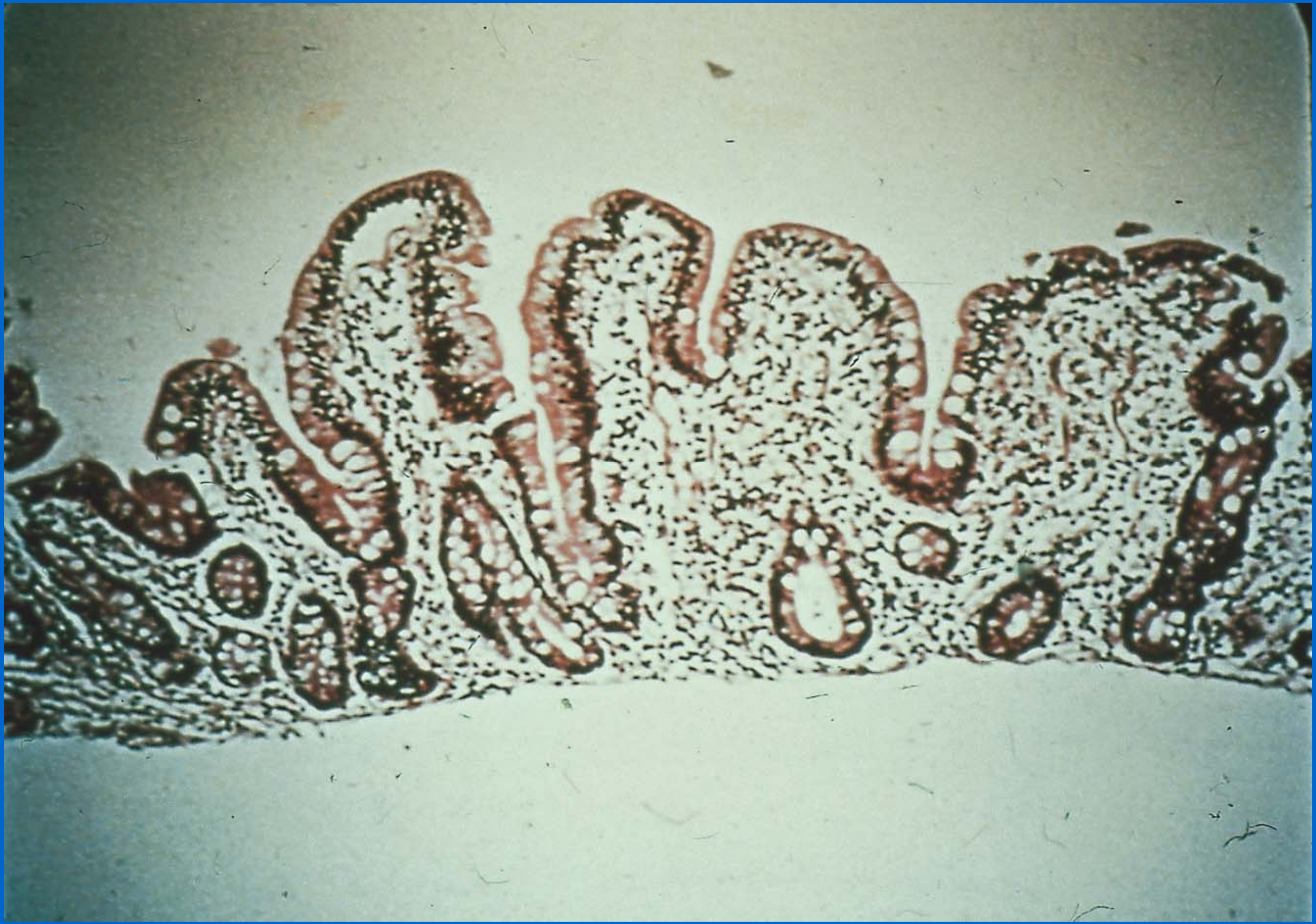

*From: Manninen V, et al. Lancet 1973;1:398-99.

# Factors Affecting RATE and EXTENT of Drug Absorption



# Normal Intestinal Villi

# Broad Intestinal Villi in a Patient with SPRUE



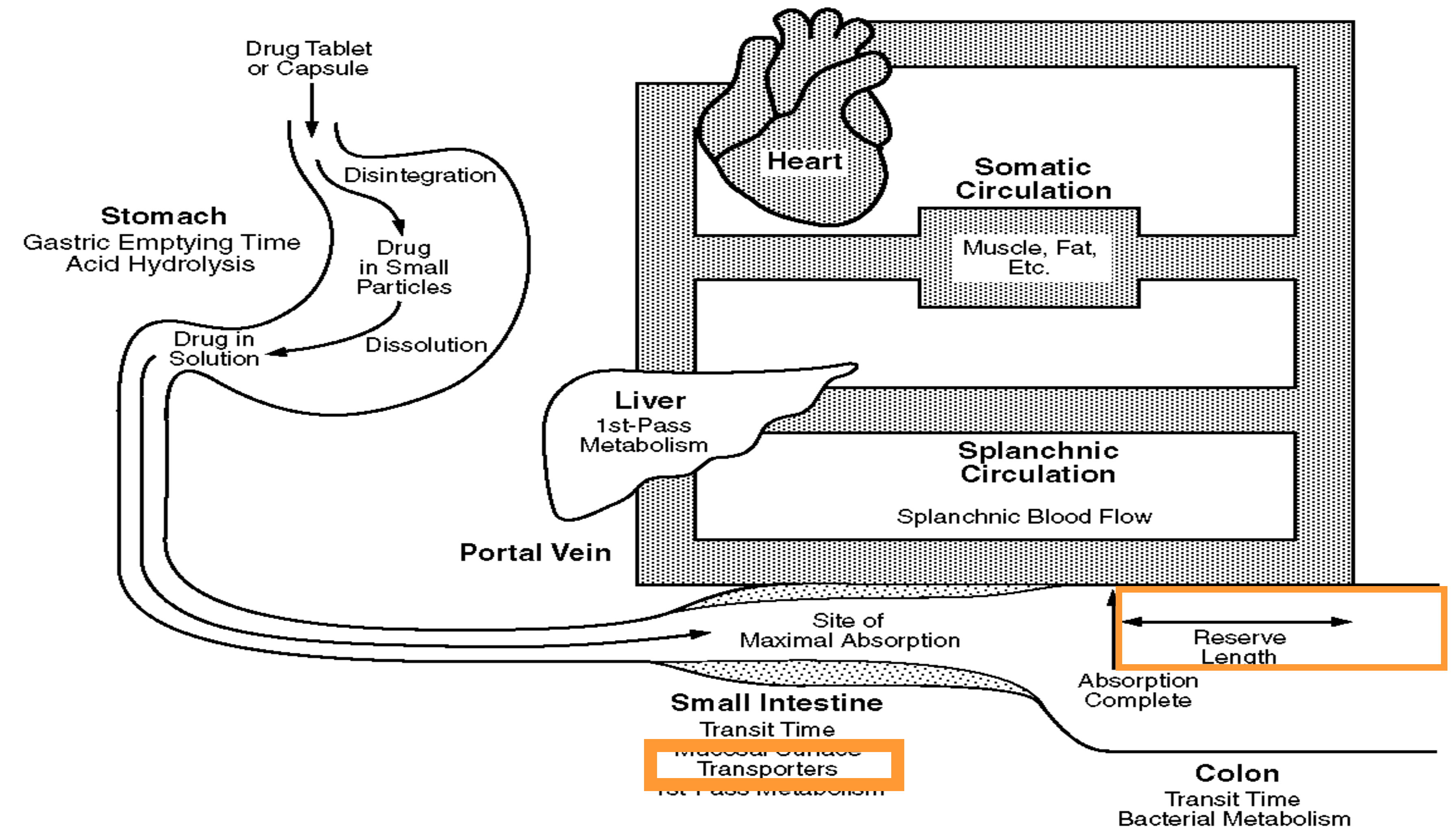
# Digoxin Levels in Patients with INTESTINAL MALABSORPTION*

| DOSE FOR BOTH GROUPS = 0.25 mg/day. | CONTROLS | MALABSORPTION |
|---|---|---|
| [DIGOXIN] (ng/mL) | 1.3 ± 0.3 | 0.4 ± 0.3 |
| URINE D-XYLOSE EXCRETION (gm/5 hr) | 5 – 8† | 1.1 – 4.1 |

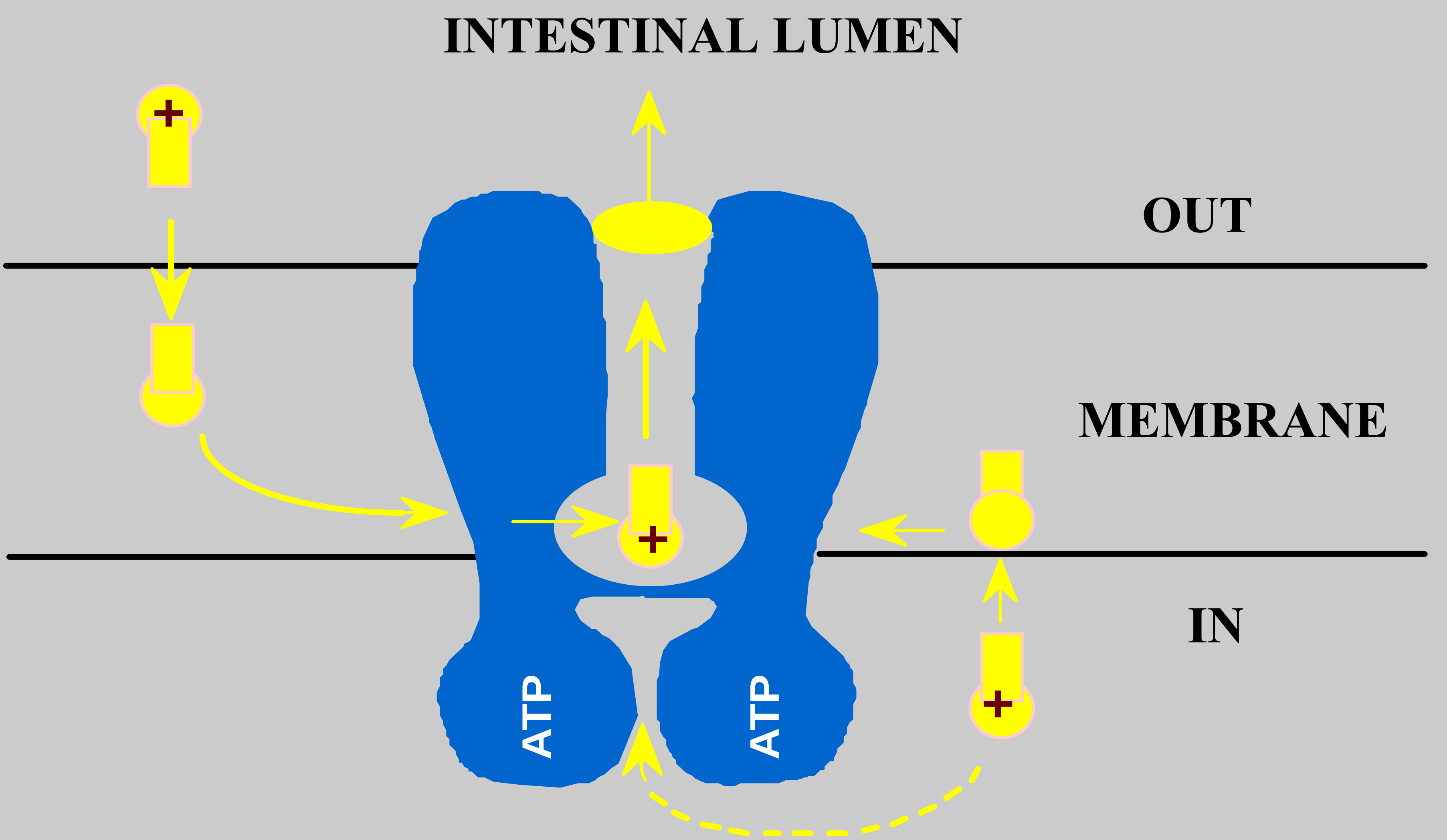
† NORMAL RANGE

* From: Heizer WD, et al. N Engl J Med 1971;285:257-9.

# Factors Affecting RATE and EXTENT of Drug Absorption



# P-GLYCOPROTEIN EFFLUX PUMP

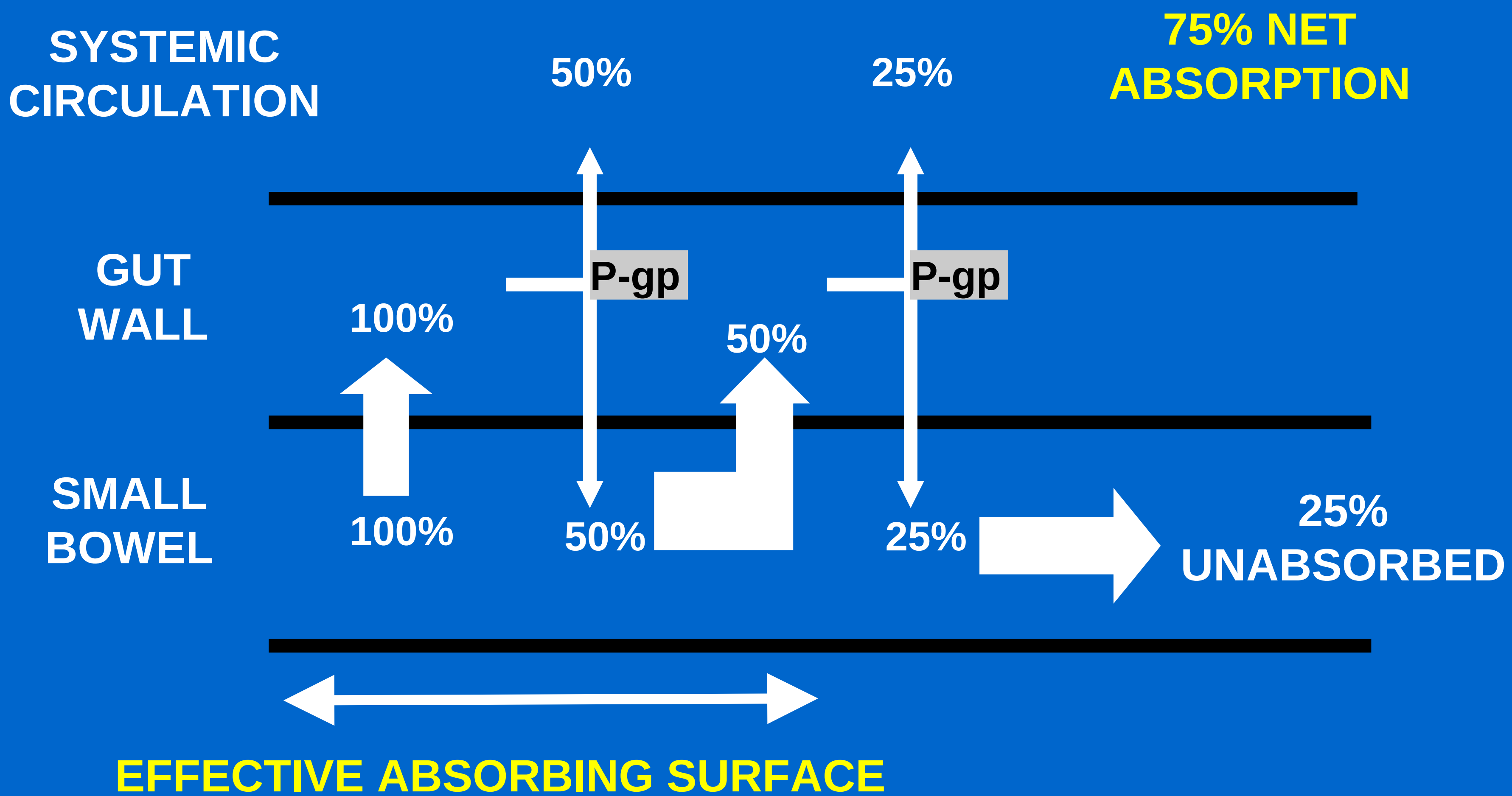



SLIDE COURTESY OF M. GOTTESMAN

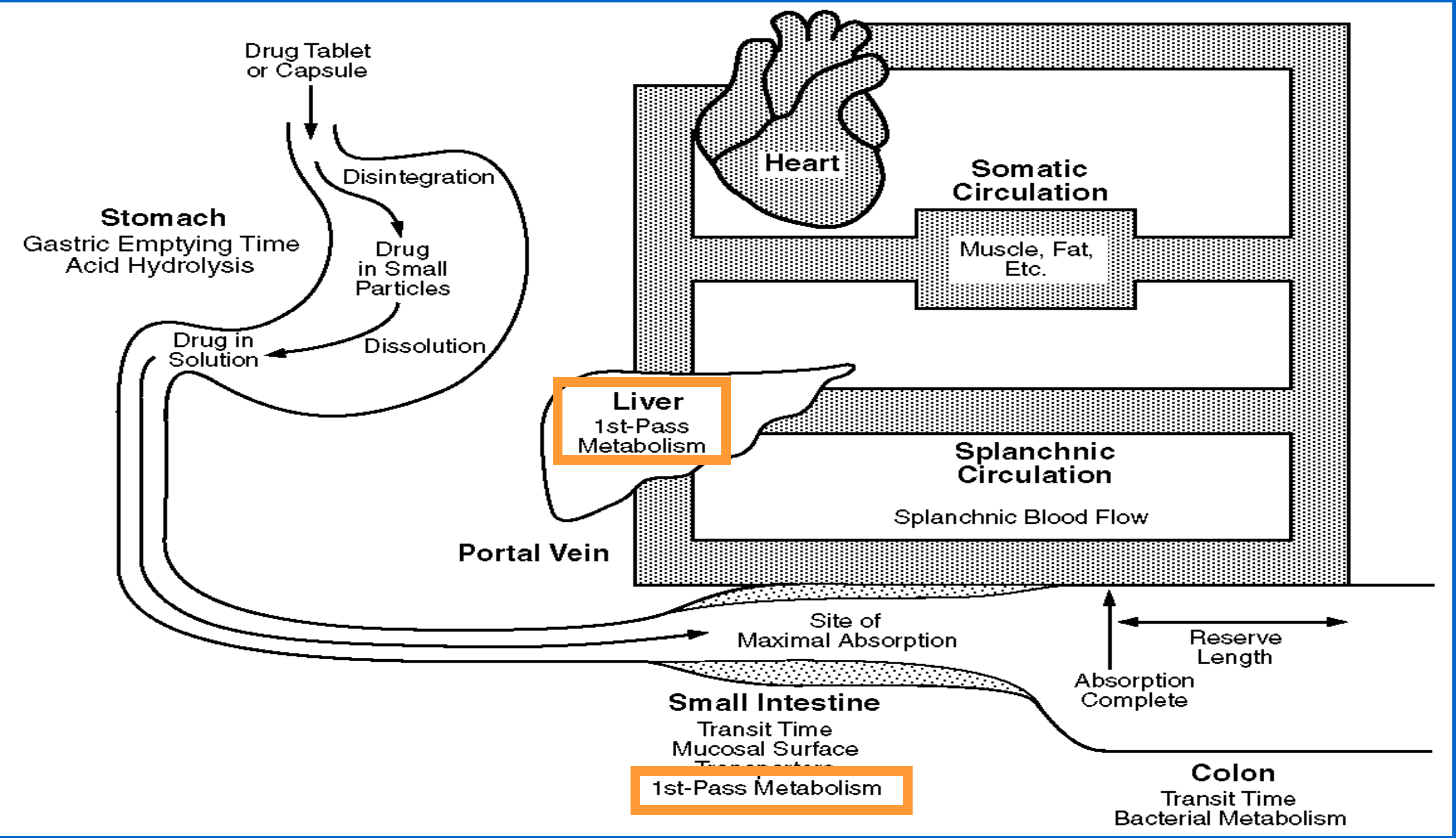
# BIOAVAILABILITY OF SOME *P-GLYCOPROTEIN SUBSTRATES*

| > 70% ABSORPTION | | 30% - 70% ABSORPTION | | < 30% ABSORPTION | |
|---|---|---|---|---|---|
| DRUG | F % | DRUG | F % | DRUG | F % |
| PHENOBARBITAL | 100 | DIGOXIN | 70 | CYCLOSPORINE | 28 |
| LEVOFLOXACIN | 99 | INDINAVIR | 65 | TACROLIMUS | 25 |
| METHADONE | 92 | CIMETIDINE | 60 | MORPHINE | 24 |
| PHENYTOIN | 90 | CLARITHROMYCIN | 55 | VERAPAMIL | 22 |
| METHYLPREDNISOLONE | 82 | ITRACONAZOLE | 55 | NICARDIPINE | 18 |
| TETRACYCLINE | 77 | AMITRIPTYLINE | 48 | SIROLIMUS | 15 |
| | | DILTIAZEM | 38 | SAQUINAVIR | 13 |
| | | ERYTHROMYCIN | 35 | ATORVASTATIN | 12 |
| | | CHLORPROMAZINE | 32 | DOXORUBICIN | 5 |

# > 70% BIOAVAILABILITY OF SOME P-GLYCOPROTEIN SUBSTRATES



# FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION



# Sites of FIRST-PASS Elimination

- **INTESTINAL MUCOSA**

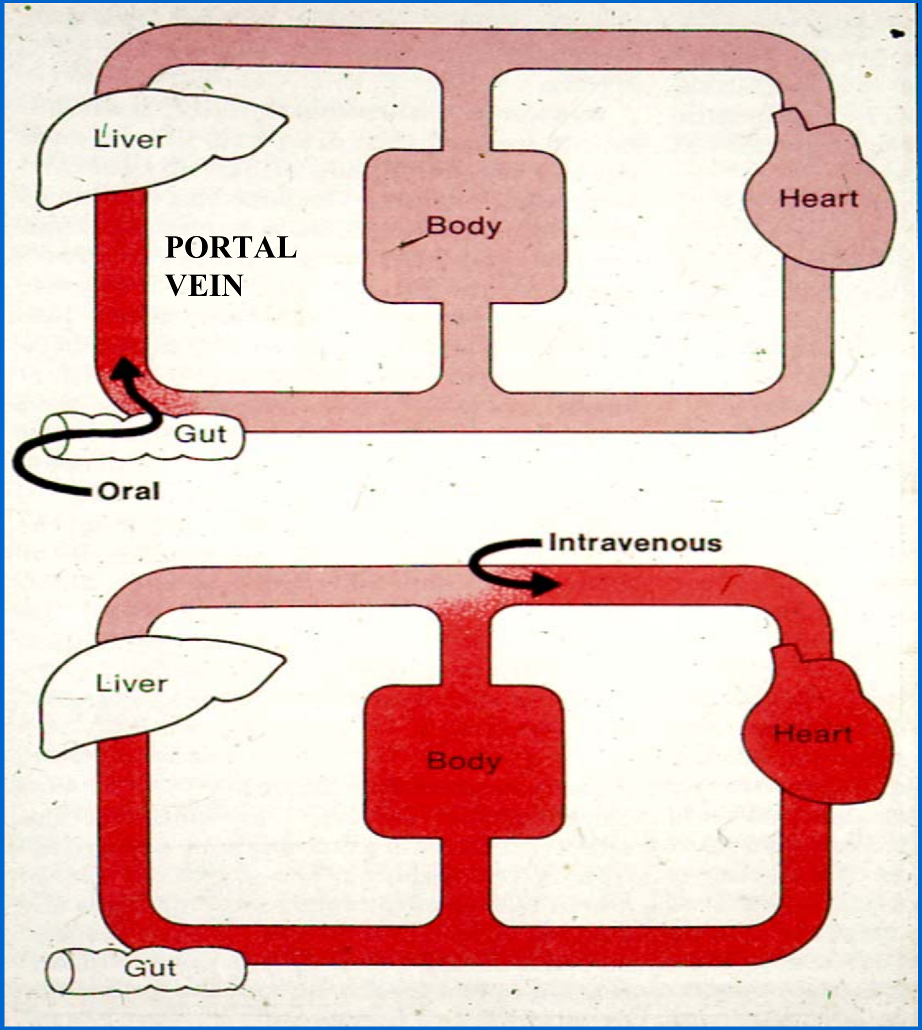
  **CYP Enzymes**

  **P-Glycoprotein**

- **LIVER**

  **CYP Enzymes**

# FIRST-PASS METABOLISM

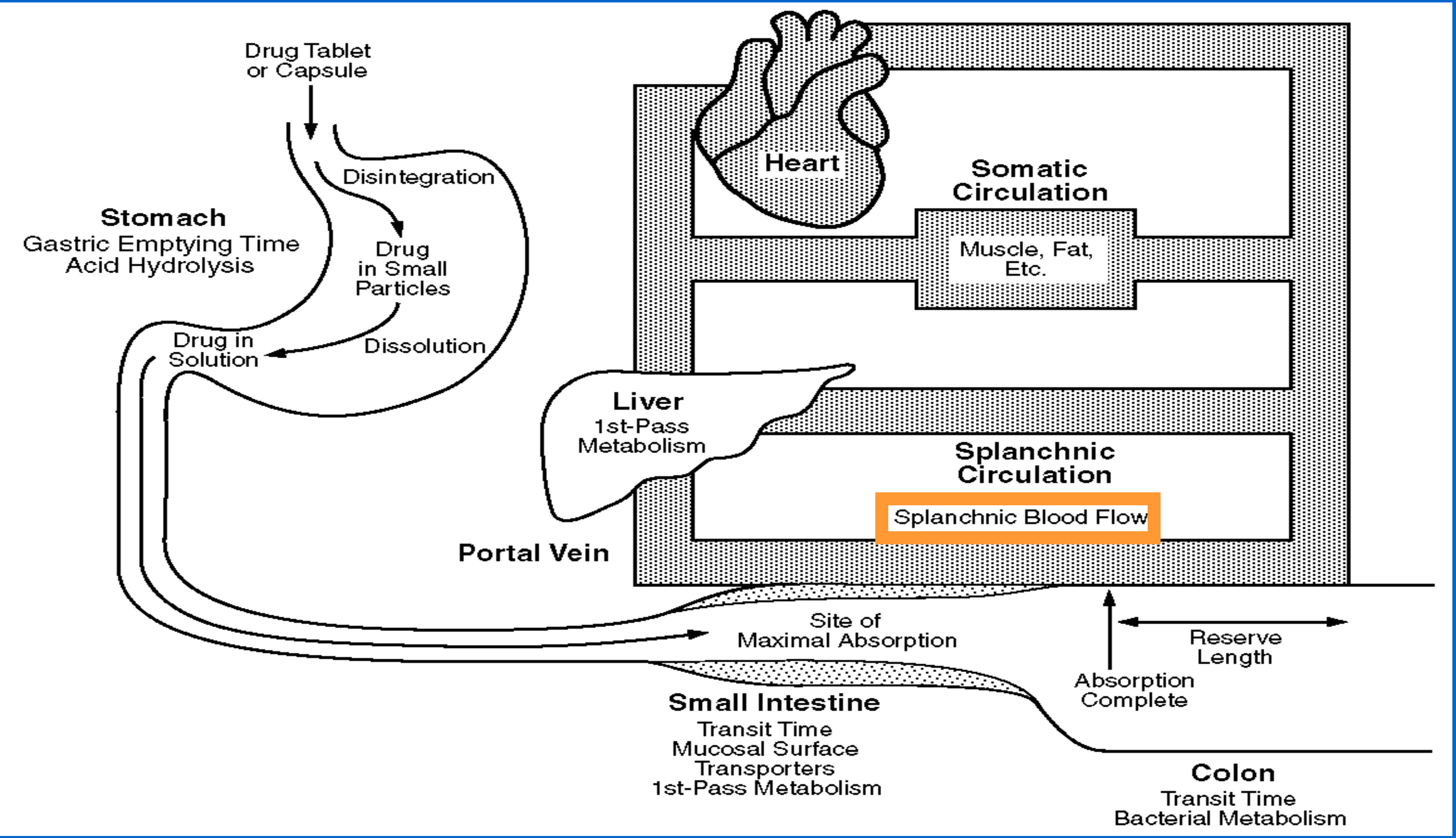


# First-Pass Metabolism
# ± P-Glycoprotein Transport

| | |
|---|---|
| ALDOSTERONE | MORPHINE* |
| CYCLOSPORINE* | NORTRIPTYLINE |
| ISOPROTERENOL | ORGANIC NITRATES |
| LIDOCAINE | PROPRANOLOL |

* Known P-Glycoprotein Substrates

# Factors Affecting RATE and EXTENT of Drug Absorption



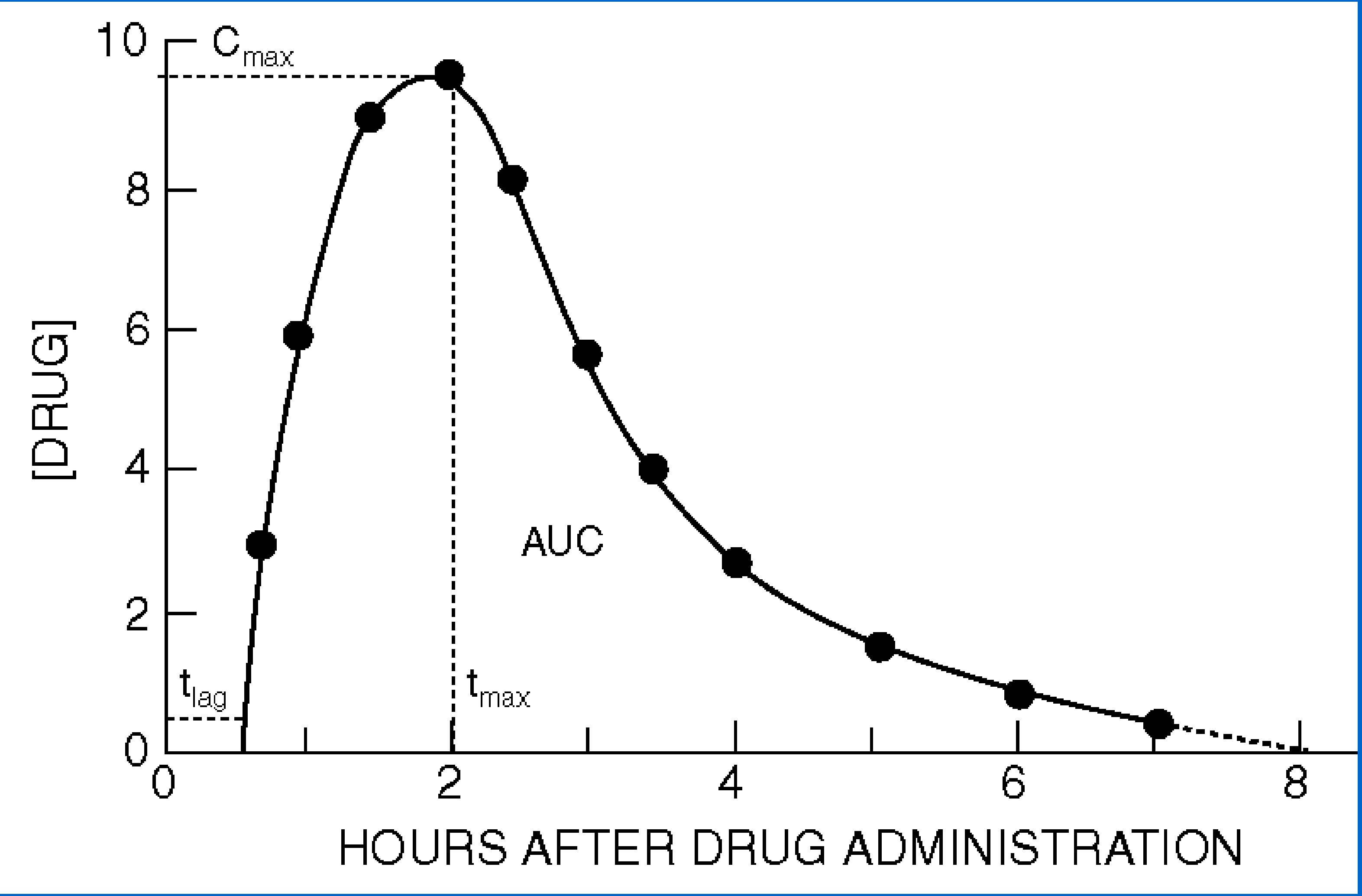
# GOALS of Drug Absorption and Bioavailability Lecture

- Factors Affecting Drug Absorption
- ESTIMATION OF BIOAVAILABILITY
- Clinical Significance of Differences in Bioavailability
- Prediction of Bioavailability

# BIOAVAILABILITY

**BIOAVAILABILITY is the *RELATIVE AMOUNT (F)* of a drug dose that reaches the systemic circulation unchanged and the *RATE* at which this occurs.**

# Serum Concentration-Time Curve after a Single Oral Dose



# Significance of AUC

$$dE = CL_E \bullet C\,dt$$

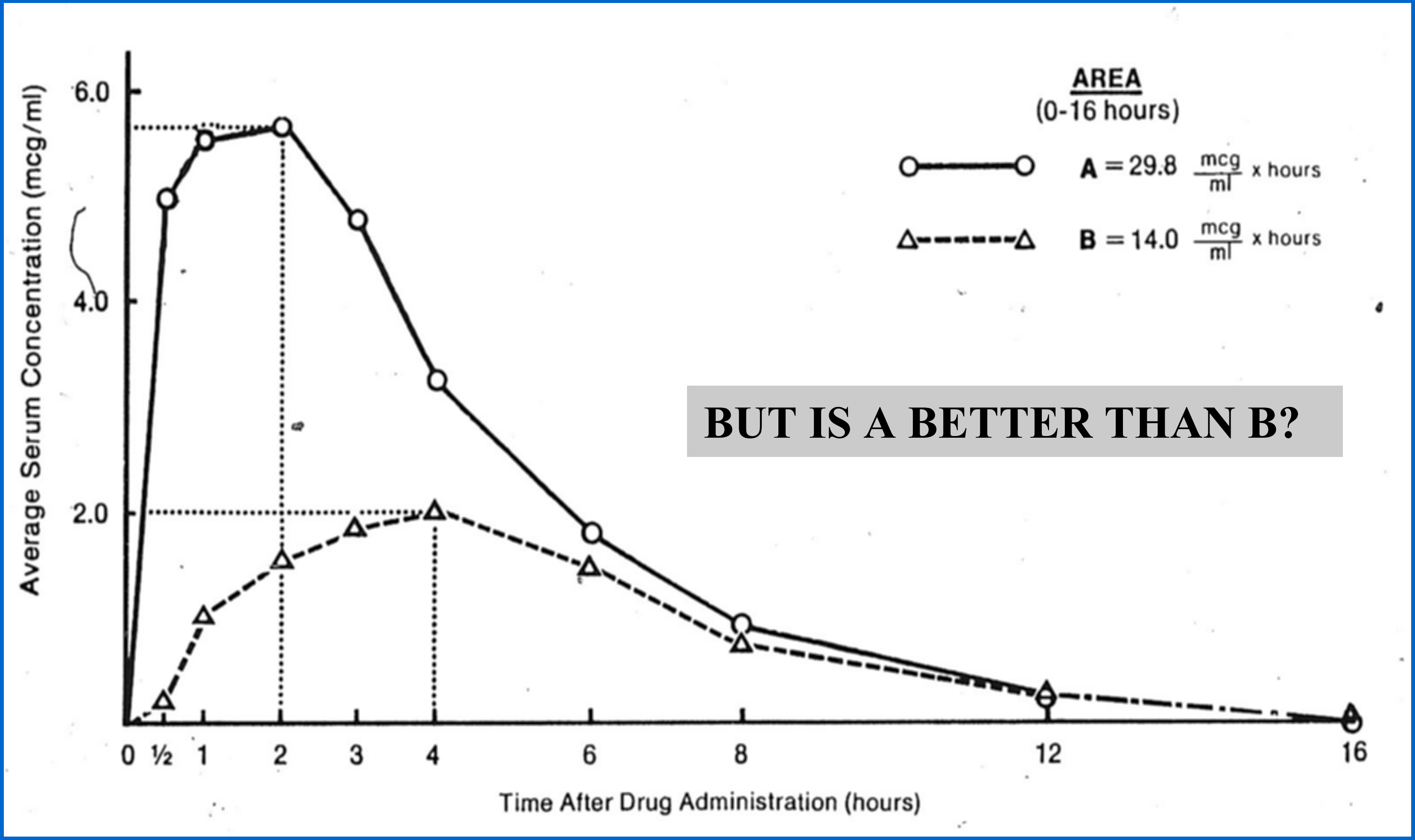
$$E = CL_E \int_0^{\infty} C\,dt$$

$$D \bullet F = CL_E \bullet AUC$$

# Calculation of AUC
# Trapezoidal Rule

From: Rowland M, Tozer TN. Clinical Pharmacokinetics. p 470.

# AUC A > B


AREA
(0-16 hours)
A = 29.8 mcg/ml x hours
B = 14.0 mcg/ml x hours
Average Serum Concentration (mcg/ml)
6.0
4.0
2.0
0
½
1
2
3
4
6
8
12
16
Time After Drug Administration (hours)
BUT IS A BETTER THAN B?

# *ABSOLUTE* Bioavailability

$$\% \text{ Absorption} = \frac{D_{IV} \bullet AUC_{oral}}{D_{oral} \bullet AUC_{IV}} \times 100$$

**Comparison here is between an ORAL and an IV Formulation**

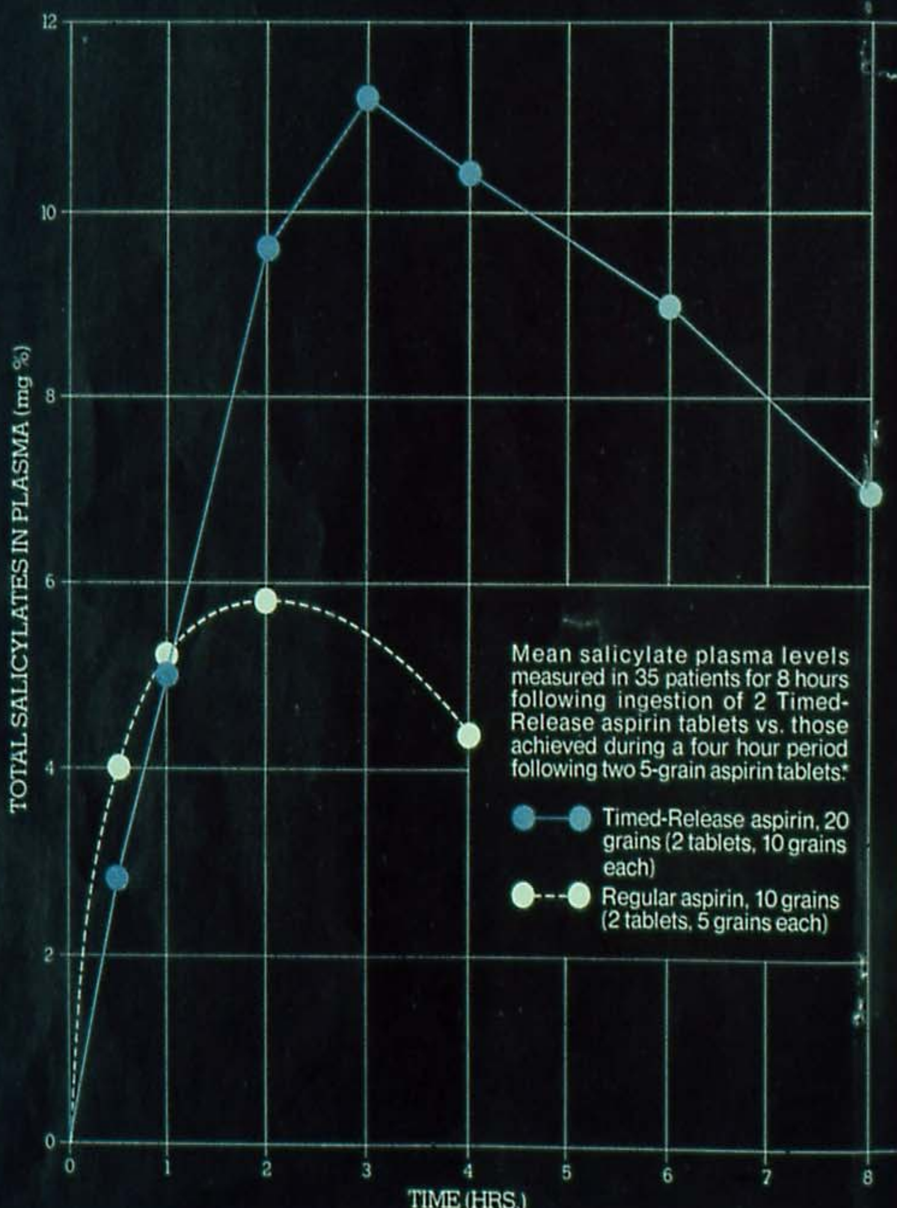
# ***RELATIVE*** **Bioavailability**

$$\%\ \text{Relative B.A.} = \frac{D_{\text{Ref.}} \bullet AUC_{\text{Test}}}{D_{\text{Test}} \bullet AUC_{\text{Ref.}}} \times 100$$

**Comparison here is between**

**2 ORAL Formulations**

# How to keep salicylate blood levels up




# ...even when your arthritis patient isn't.

A shift at bedtime from Bayer® 5-grain Aspirin to Bayer® Timed-Release Aspirin can help maintain the consistent serum salicylate levels so important for control of arthritic inflammation and pain—*without the need to interrupt sleep.*

Formulated especially for use in arthritis, this exclusive 8-hour dosage form provides 10 grains (650 mg) of microencapsulated aspirin in each tablet. While patients sleep, aspirin is released systematically into the bloodstream. Salicylate levels and anti-inflammatory activity are prolonged and patients should experience less nighttime awakening due to pain and arise freer of discouraging morning stiffness.

So during the day, when arthritis patients are up to take medication on schedule, recommend Bayer 5-grain Aspirin. But during the sleeping hours, for extended analgesic and anti-inflammatory activity, recommend Bayer Timed-Release Aspirin, 2 tablets, h.s. It provides all the advantages of aspirin ... throughout the night.

The night "shift" in arthritis therapy

**Bayer® Timed-Release Aspirin**

The Bayer Company

# *RELATIVE* Bioavailability

$$\% \text{ Relative B.A.} = \frac{D_{Ref.} \bullet AUC_{Test}}{D_{Test} \bullet AUC_{Ref.}} \times 100$$

**AUC Values have to be**

***Normalized for Dose***

# *ASSESSMENT* of Bioavailability

- AUC Estimates can be used to estimate Extent of Drug Absorption

- Recovery of Parent Drug in Urine can be used to estimate Extent of Drug Absorption

- How is ABSORPTION RATE assessed?
  - $T_{MAX}$
  - Integrated Pharmacokinetic Analysis of Absolute Bioavailability.

# Extent of Absorption from Renal Excretion of Unchanged Drug

$$\text{Since: } F \bullet D = E \quad \text{and} \quad E = \left(\frac{CL_E}{CL_R}\right) E_R$$

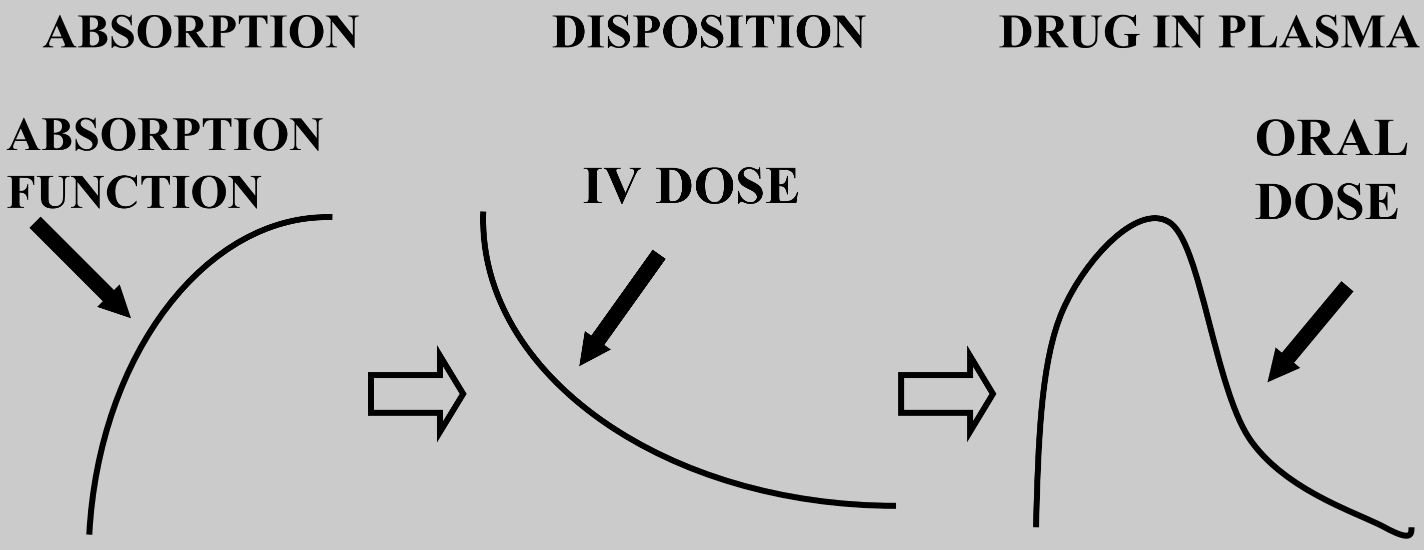
$$F \bullet D_{oral} = \left(\frac{CL_E}{CL_R}\right) E_{R(oral)} \quad \text{and} \quad D_{IV} = \left(\frac{CL_E}{CL_R}\right) E_{R(IV)}$$

$$\text{So: } \%\ \text{Absorption} = \frac{D_{IV} \bullet E_{R(oral)}}{D_{oral} \bullet E_{R(IV)}} \text{ X } 100$$

# *ASSESSMENT* OF Bioavailability

- AUC Estimates Can Be Used to Estimate Extent of Drug Absorption.
- Recovery of Parent Drug in Urine Can Be Used to Estimate Extent of Drug Absorption.
- HOW IS ABSORPTION RATE ASSESSED?
  - $T_{MAX}$
  - Integrated Pharmacokinetic Analysis of Absolute Bioavailability.

# INTERACTION OF DRUG ABSORPTION AND DISPOSITION PROCESSES




$$G(t) * H(t) = X(t)$$

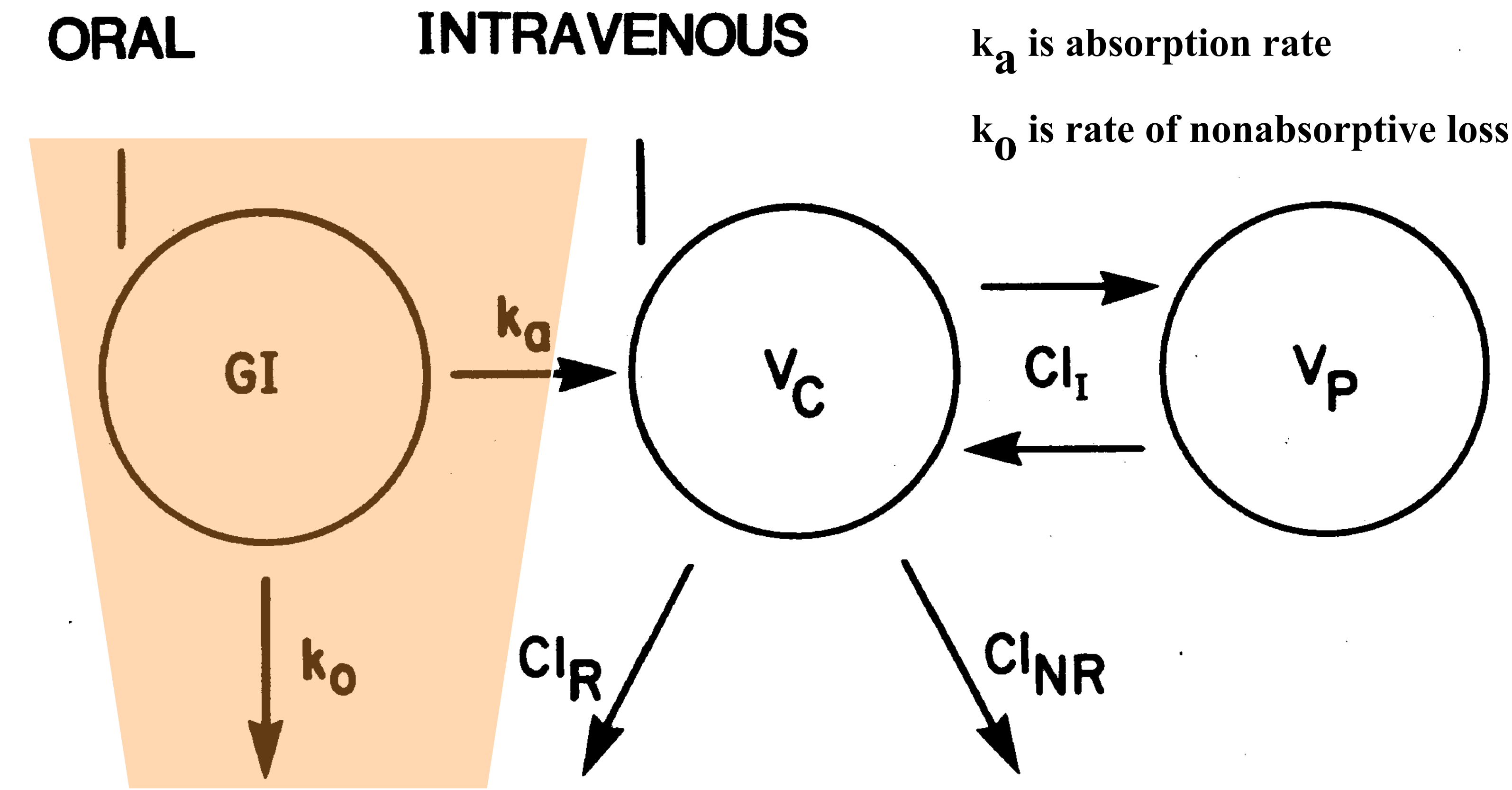
# THE OPERATION OF CONVOLUTION

**INTEGRAL FORM :** $X(t) = \int_0^t G(\tau) \bullet H(t-\tau)\,d\tau$

**TIME DOMAIN :** $X(t) = G(t) * H(t)$

**SUBSIDIARY EQUATION :** $x(s) = g(s) \bullet h(s)$

# MODEL Used to Analyze Kinetics of Drug Absorption




$k_a$ is absorption rate

$k_o$ is rate of nonabsorptive loss

# Calculation of Bioavailability from First-Order Absorption Model

$$F = \frac{k_a}{k_a + k_o}$$

# Methods for Assessment of *ABSOLUTE* BIOAVAILABILITY

- **CONVENTIONAL:**

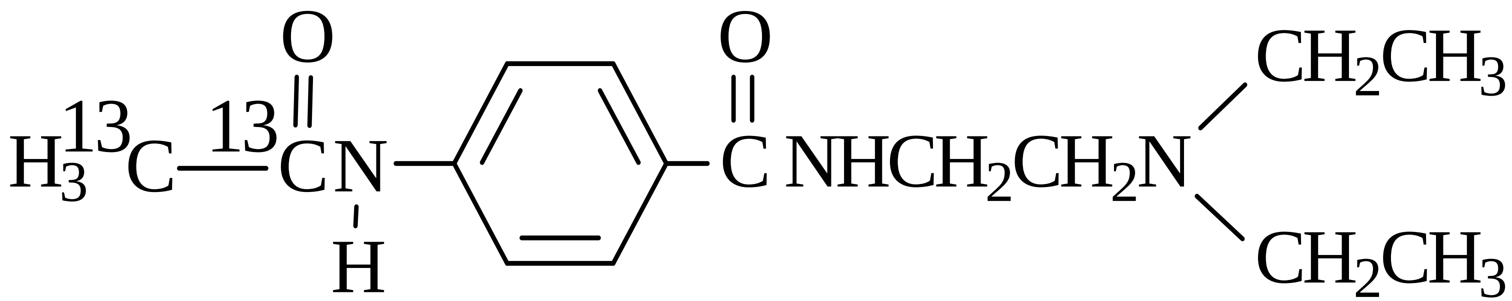
  **IV and ORAL doses given on two separate occasions.**

  - **Requires two study sessions**
  - **Requires two sets of blood samples**
  - **Assumes no change in disposition parameters between studies**

- **STABLE ISOTOPE:**

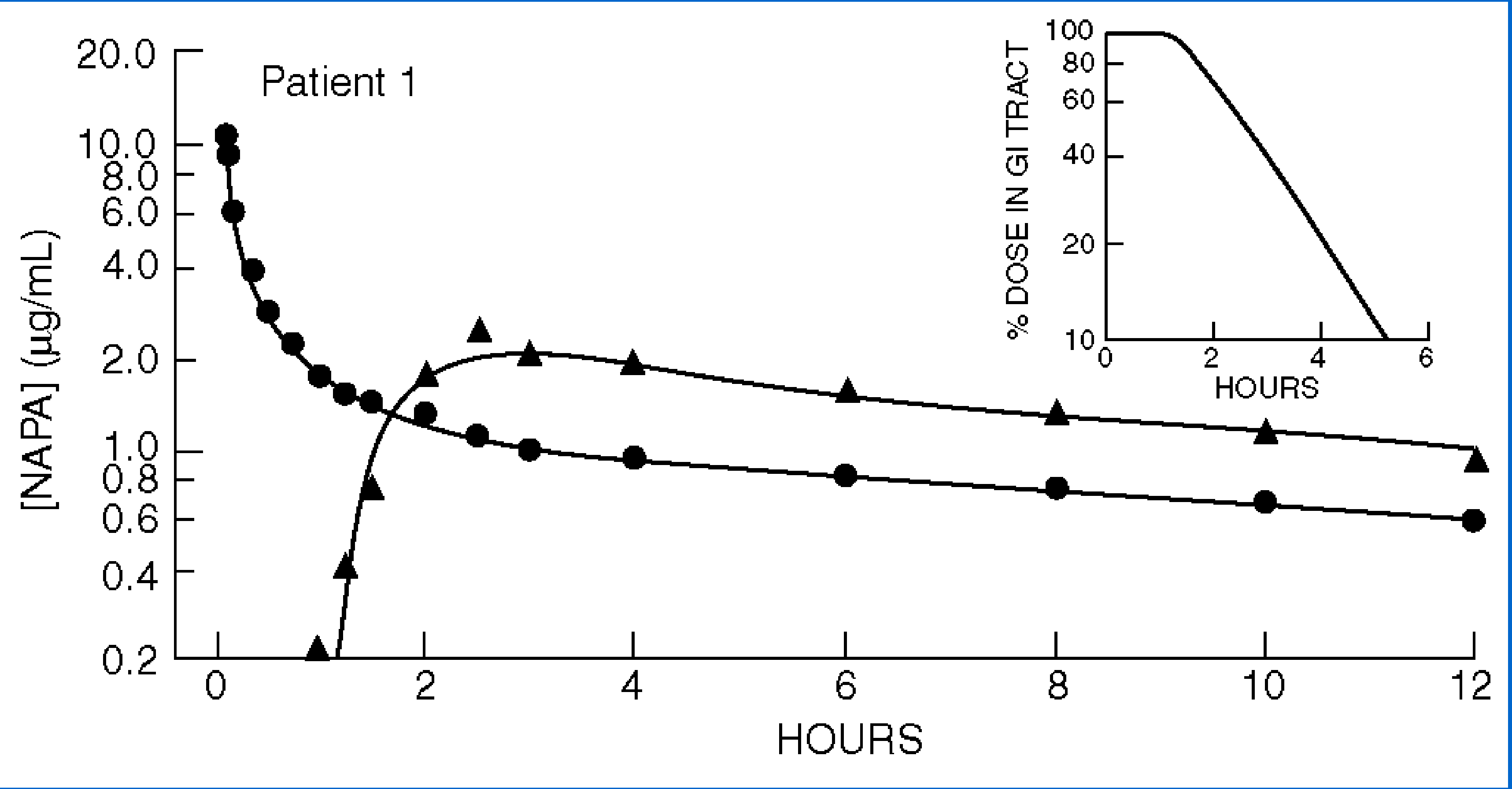
  - **One study and set of blood samples**
  - **Special synthesis requirements**
  - **Mass Spectrometer Assay required**

# NAPA-$^{13}C_2$



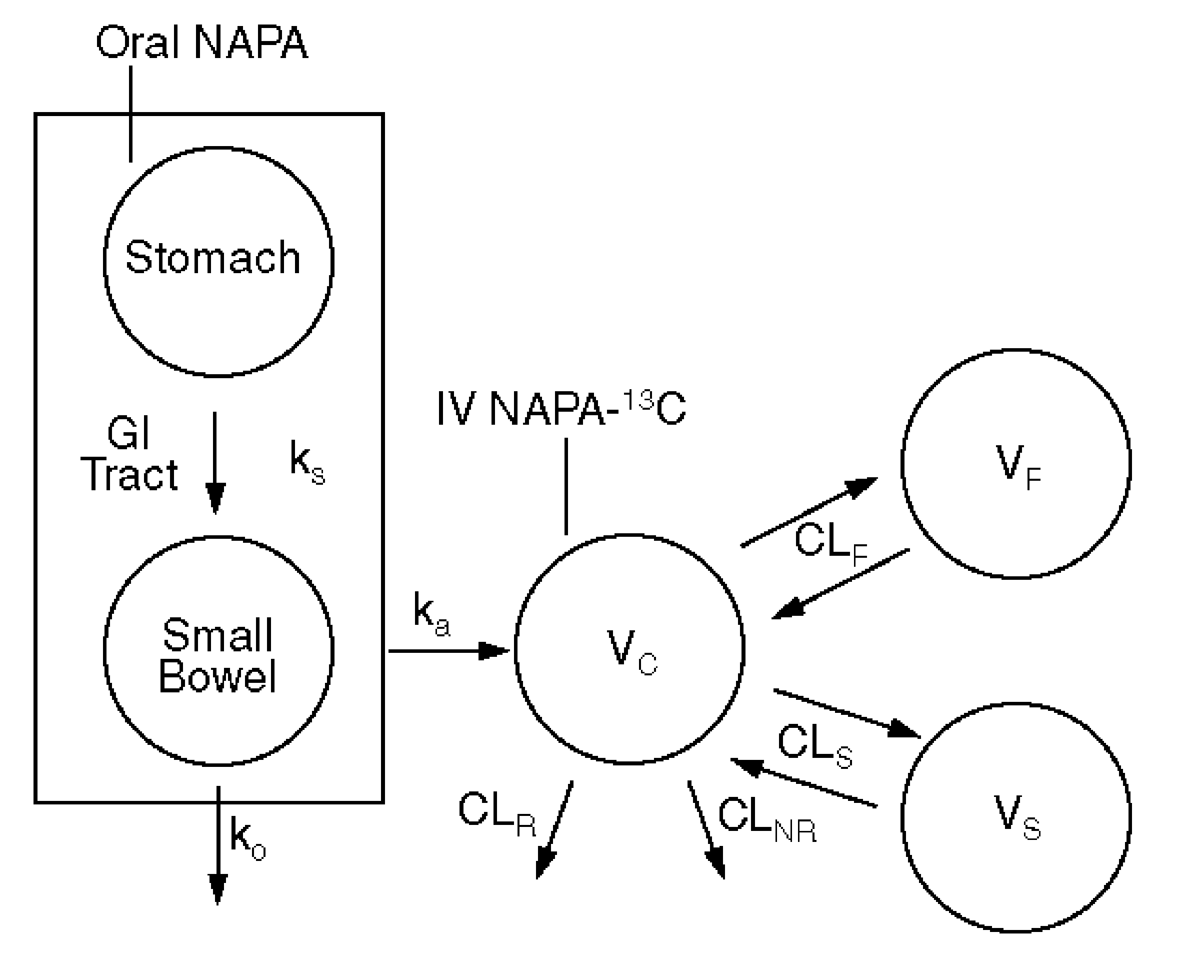

***N*** **- ACETYLPROCAINAMIDE ( NAPA -$^{13}C_2$)**

# Simultaneous Administration of Oral NAPA and IV NAPA-C[13]*




* From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.

# MODEL Used to Analyze Oral NAPA and IV NAPA-C13 Kinetics*



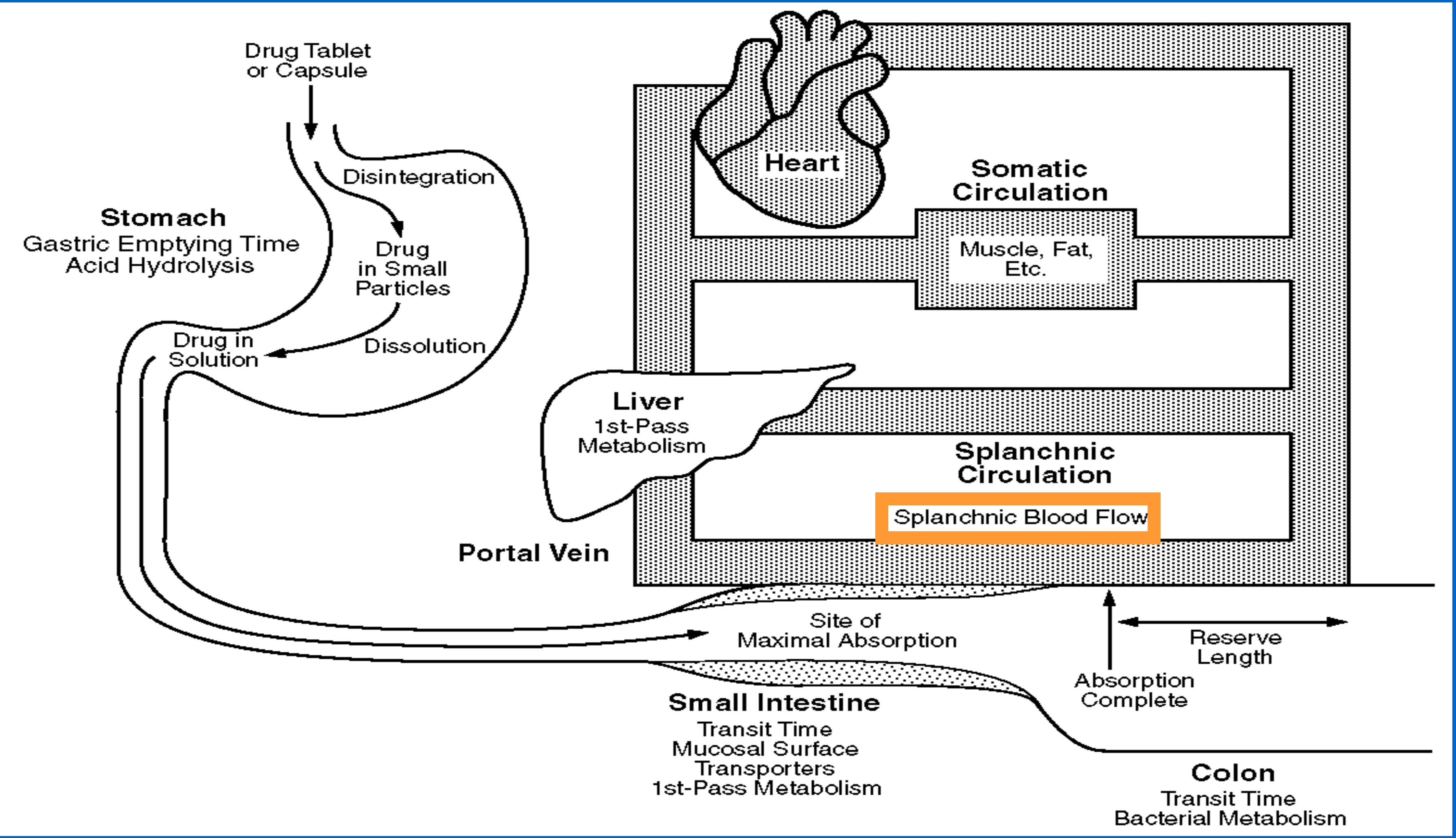

* From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.

# BIOAVAILABILITY Estimates From Kinetic Analysis and URINE RECOVERY

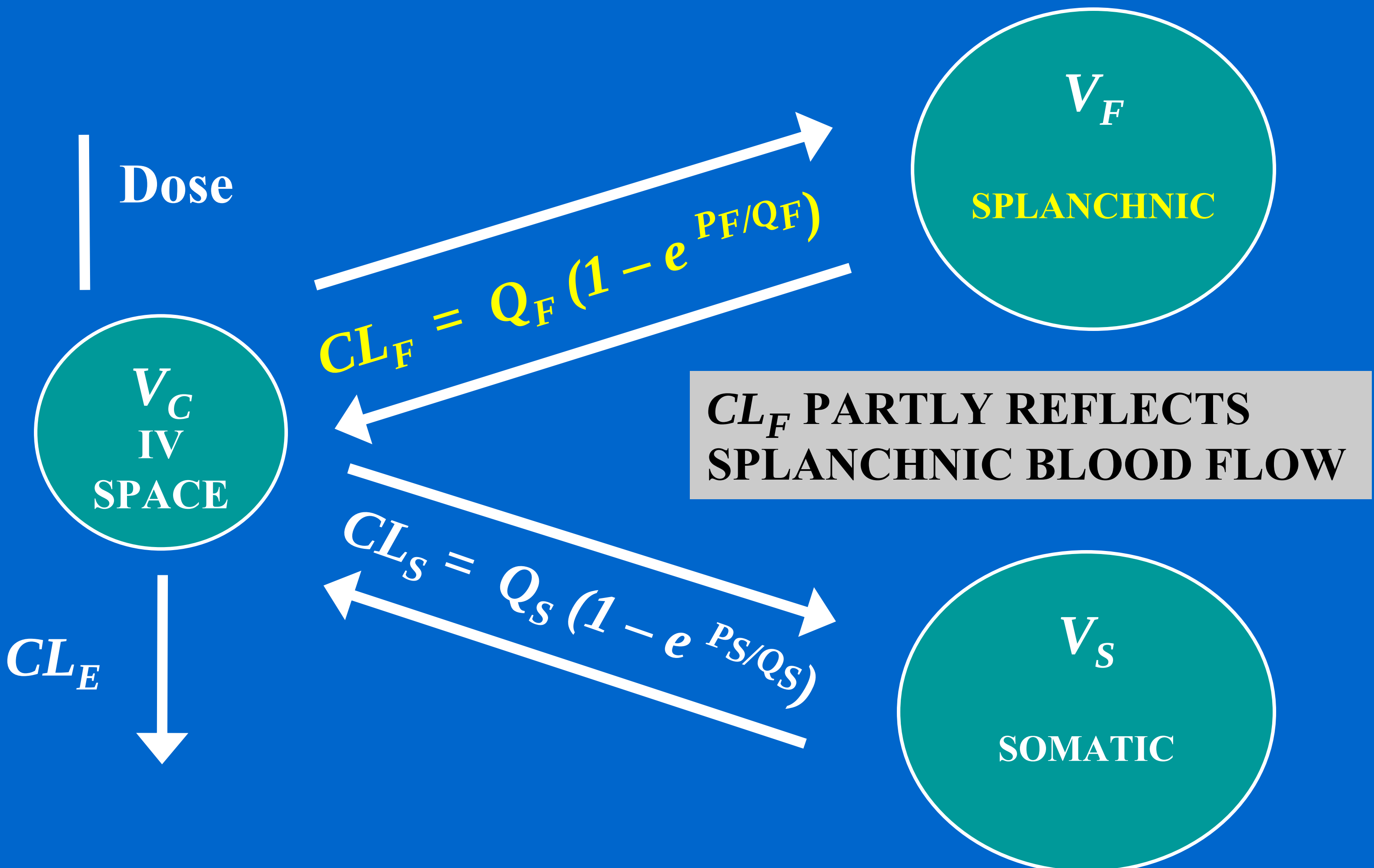
| PATIENT NUMBER | KINETIC ANALYSIS (%) | NAPA RECOVERY IN URINE* (%) |
|---|---|---|
| 1 | 66.1 | 65.9 |
| 2 | 92.1 | 92.1 |
| 3 | 68.1 | 69.9 |
| 4 | 88.2 | 73.1 |
| 5 | 75.7 | 75.6 |

* Corrected for absorption lag time.

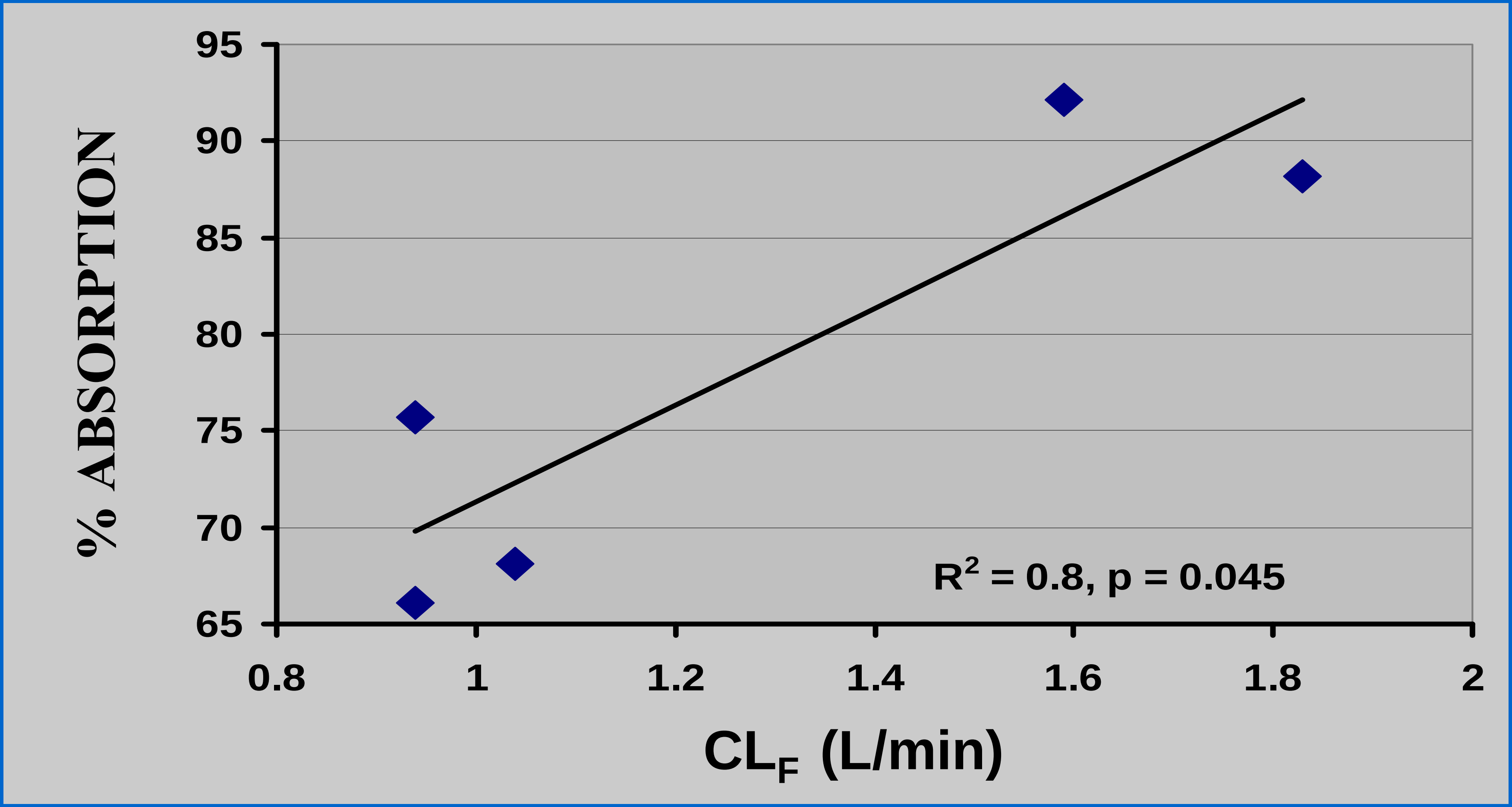
# Factors Affecting RATE and EXTENT of Drug Absorption



# NAPA PK Model After IV Dose



# Relationship Between $CL_F$ and Extent of NAPA Absorption*




* From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.

# THOUGHTS About
# Absolute Bioavailability Studies

- **Absolute Bioavailability is usually studied in Healthy Subjects, *NOT* in the *Patient Population* *for whom the drug is intended*.**
- **The Stable Isotope Method is ideally suited for studies in *Special Populations* *(e.g. Pediatrics, Pregnant Women, other)***

# GOALS of Drug Absorption and Bioavailability Lecture

- Factors Affecting Drug Absorption
- Estimation of Bioavailability
- Clinical Significance of Differences in Bioavailability
- Prediction of Bioavailability

# *RELATIVE* Bioavailability Terms

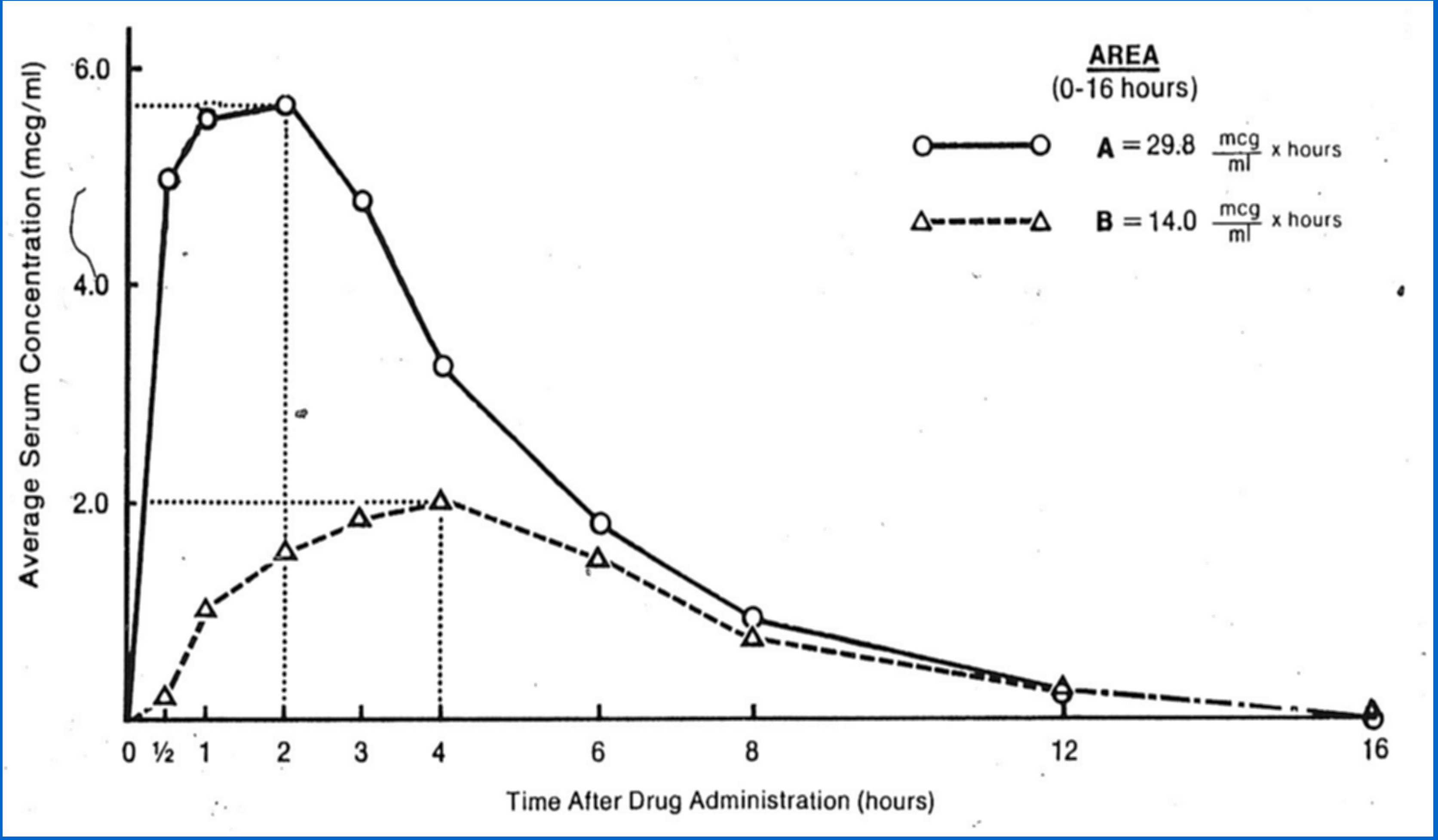
**Bioequivalence:** AUC and Cmax within 80% - 125% of reference compound.

***Bioinequivalence:*** **Greater difference in bioavailability.**

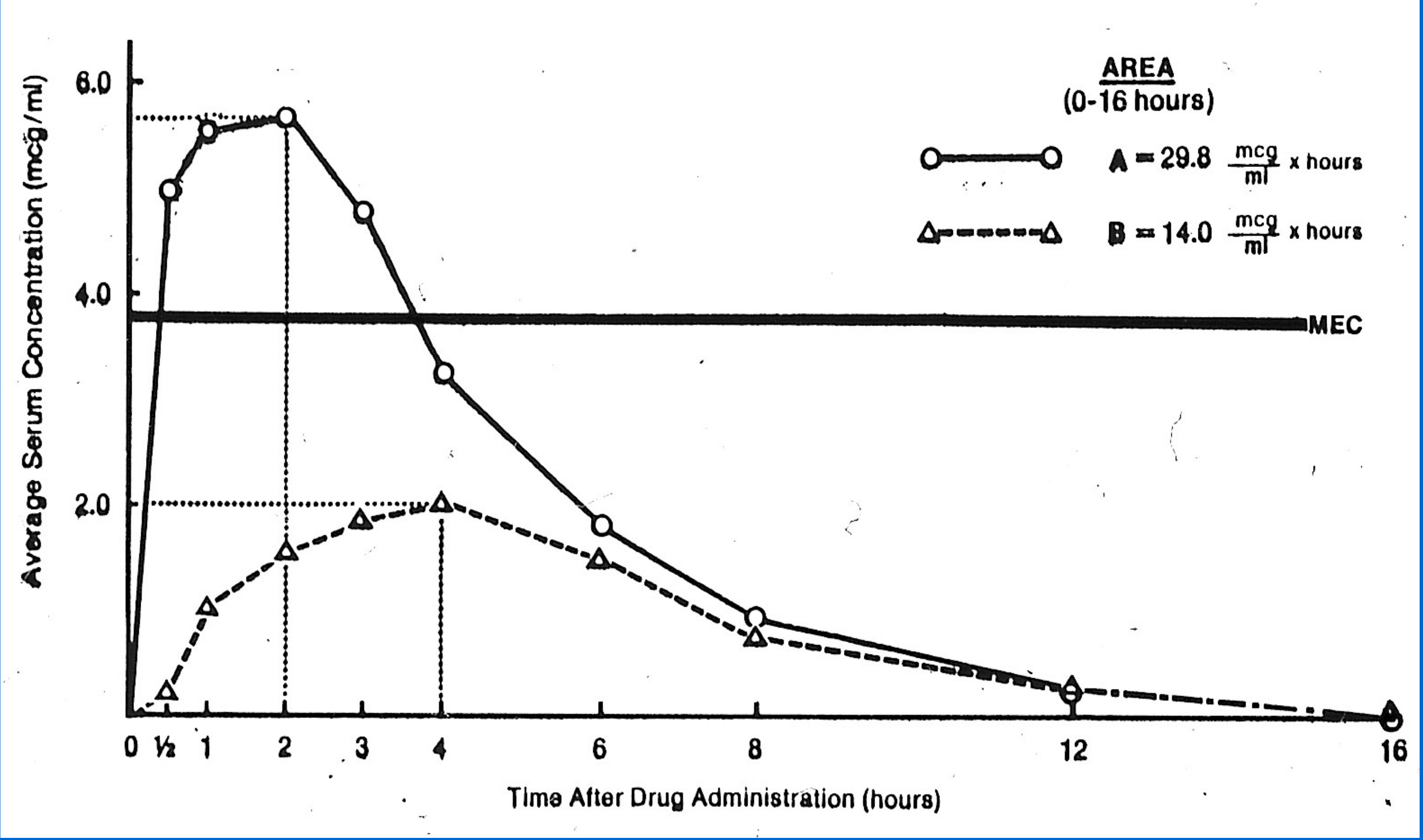
**Therapeutic Equivalence:** Similar clinical effectiveness and safety.

***Therapeutic Inequivalence:*** **Important clinical difference in bioavailability.**

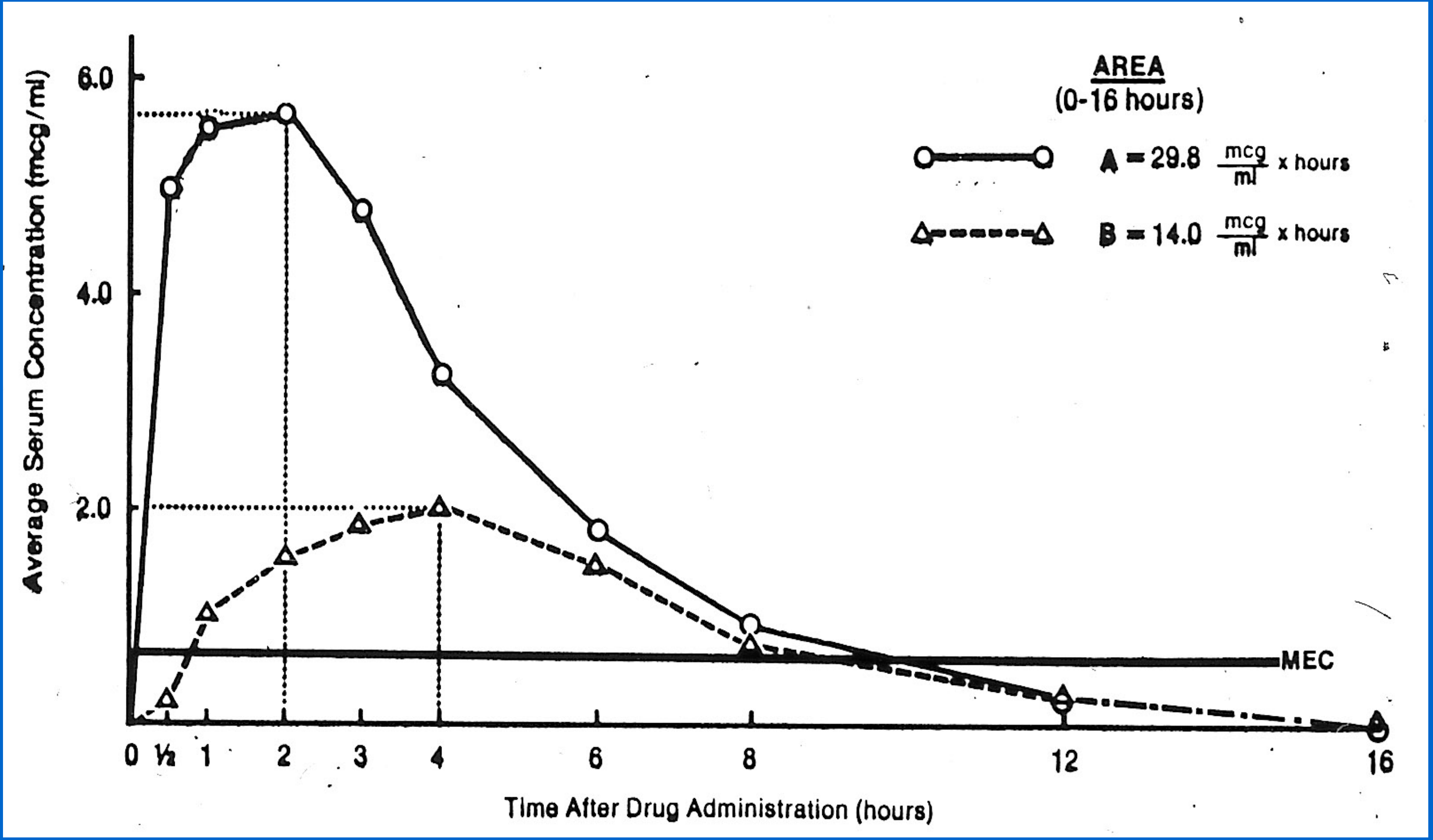
# AUC A > B: Therapeutic Significance?



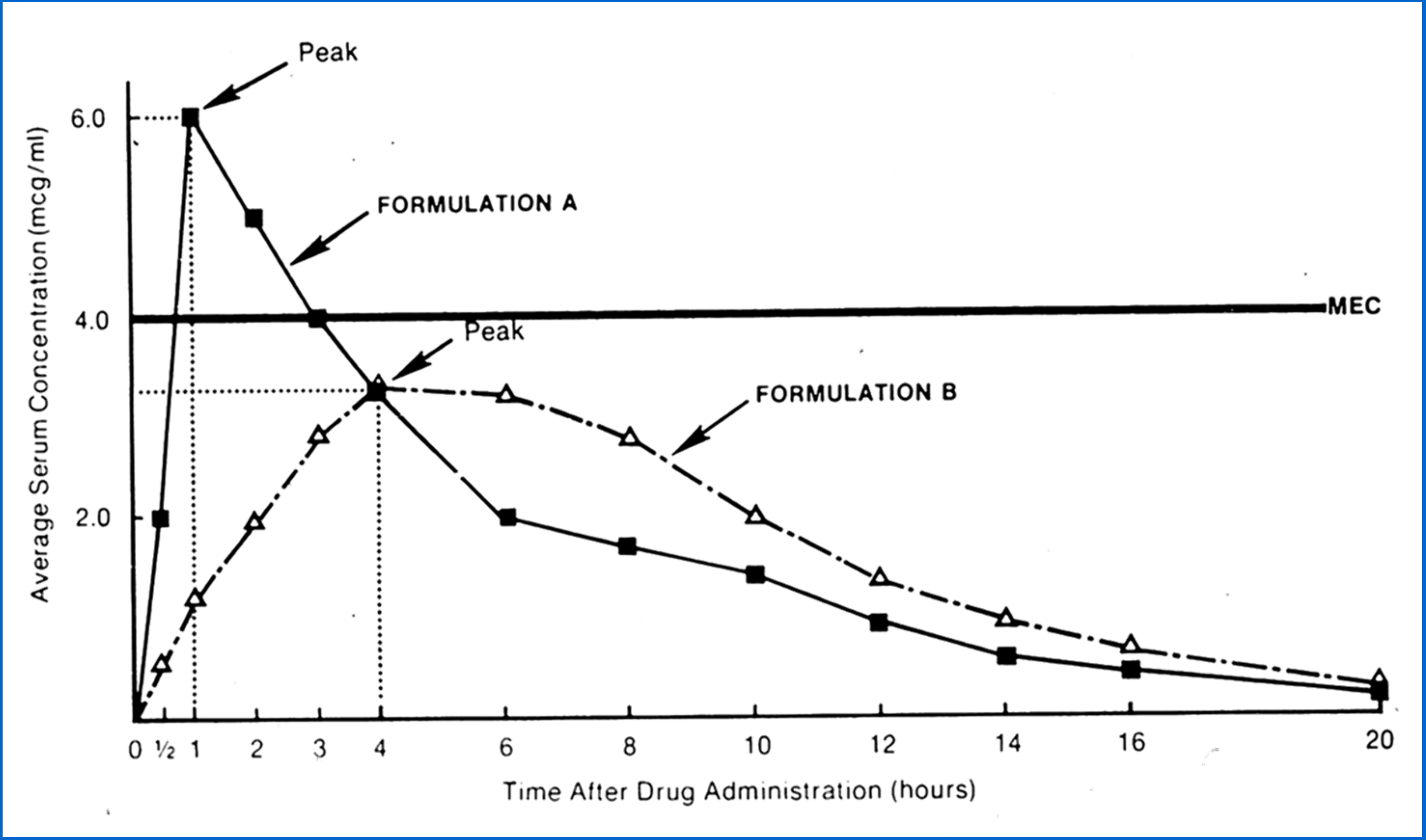
# AUC A > B: B Ineffective



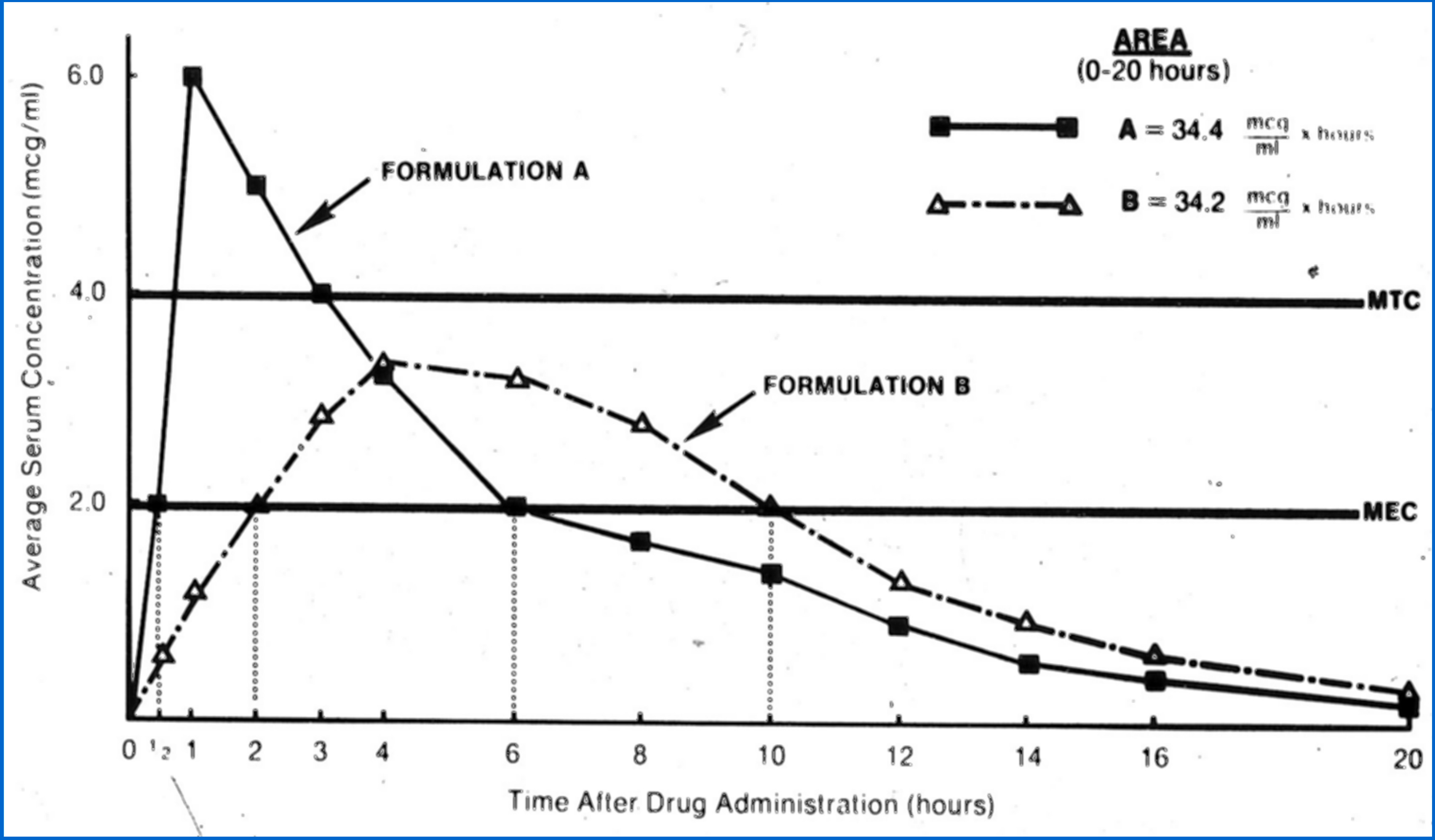
# AUC A > B:
# A and B Equally Effective



# Equal AUC but Different $K_a$: B is Ineffective



# Equal AUC but Different $K_a$:
# A is Toxic



# *RELATIVE* BIOAVAILABILITY CONCLUSIONS

- **BIOEQUIVALENCE =**

  **THERAPEUTIC EQUIVALENCE**

- **BIOINEQUIVALENCE *NOT NECESSARILY* =**

  **THERAPEUTIC INEQUIVALENCE**

# GOALS of Drug Absorption and Bioavailability Lecture

- **Factors Affecting Drug Absorption**
- **Estimation of Bioavailability**
- **Clinical Significance**
- ***PREDICTION* of Bioavailability as part of *High-Throughput* Drug Candidate Screening**

# *WHY DRUG DEVELOPMENT FAILS*

- Unsuitable **Biopharmaceutical** Properties *
- Unsuitable **Clinical Pharmacokinetics**
- Pharmacology (PD) **Doesn't Work in Humans**
- **Unexpected Toxicity** is Encountered

* Ronald E. White, Bristol-Myers Squibb (From Good Ligands to Good Drugs, AAPS-NIGMS Symposium, February 19-21, 1998)

# *BIOPHARMACEUTIC* DRUG CLASSIFICATION *

**CLASS I:**

**High Solubility-High Permeability**

**CLASS II:**

**Low Solubility-High Permeability**

**CLASS III:**

**High Solubility-Low Permeability**

**CLASS IV:**

**Low Solubility-Low Permeability**

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

# *Three CRITICAL* Biopharmaceutical Properties

- **Drug Solubility *Relative* to Dose**

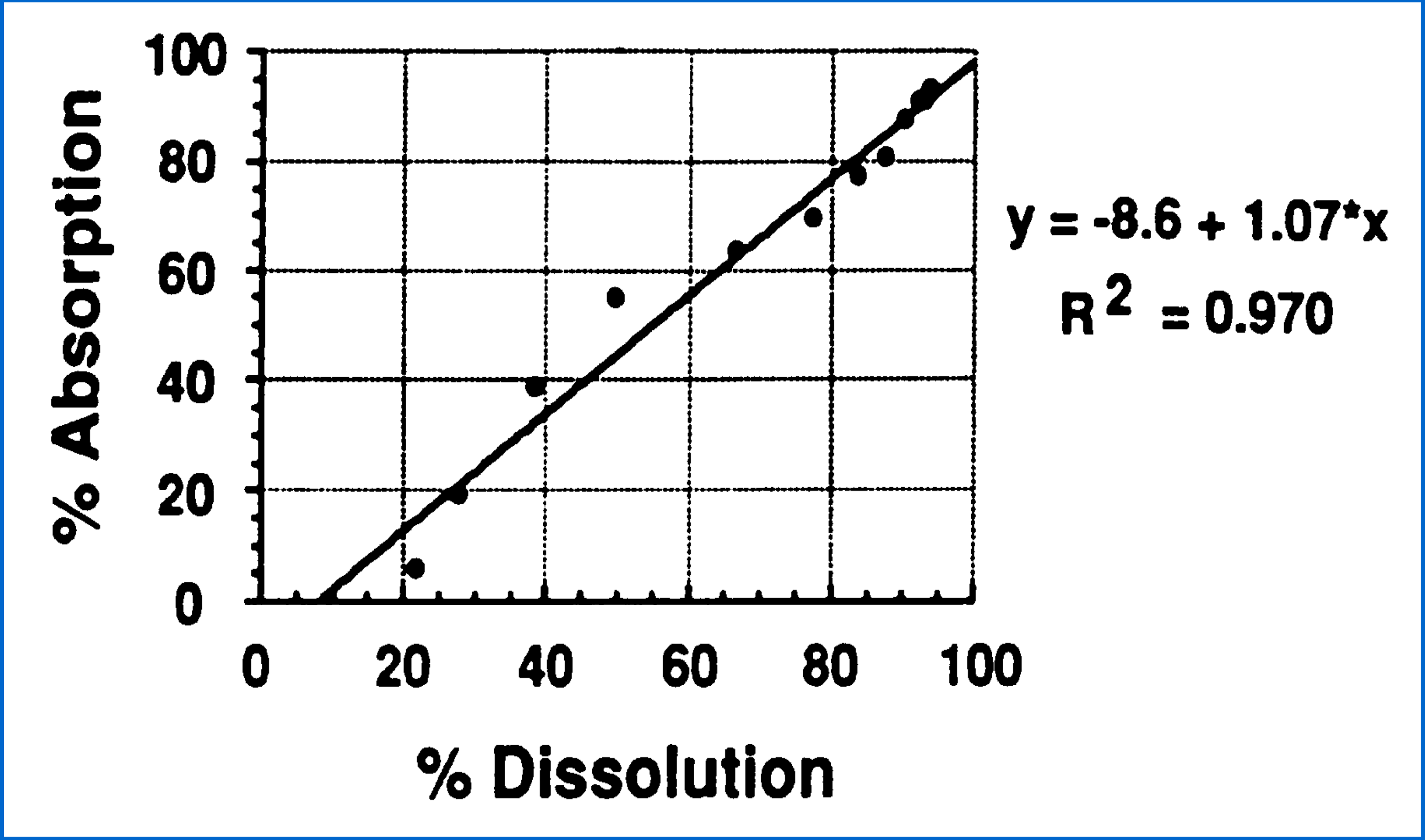
  **GOOD = Highest Dose in 250 mL $H_20$, pH 1.0-7.5**

- **Dissolution Rate of Formulation**

  **GOOD = 85% Dissolution in 15 min**

- **Intestinal Permeability of Drugs**

# *CORRELATION* of Rates of Drug *DISSOLUTION* and Oral *ABSORPTION*

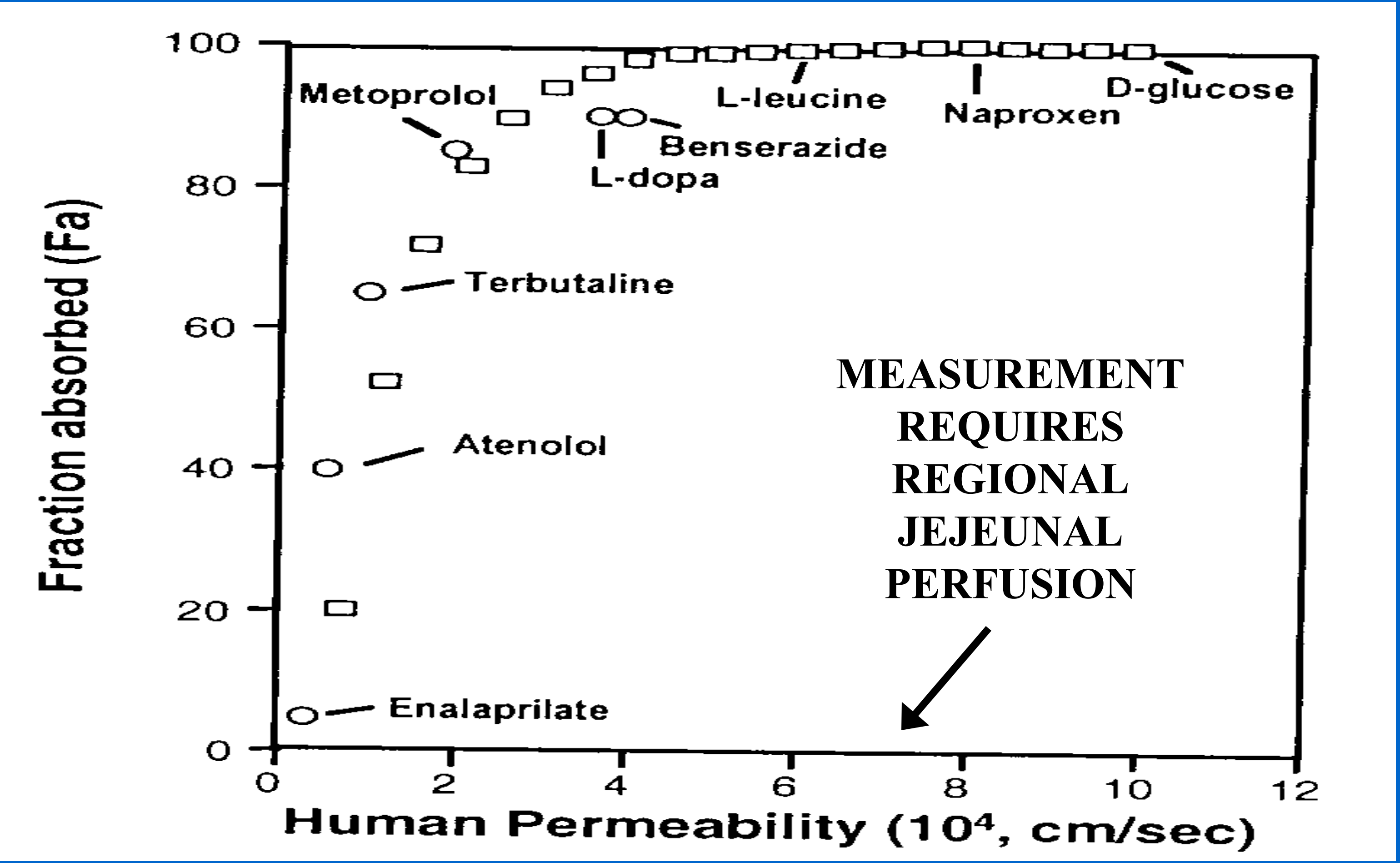



* From Rackley RJ. In Young D, Devane JG, Butler J, eds. In vitro-in vivo correlations. p. 1-15.

# *Three CRITICAL* Biopharmaceutical Properties

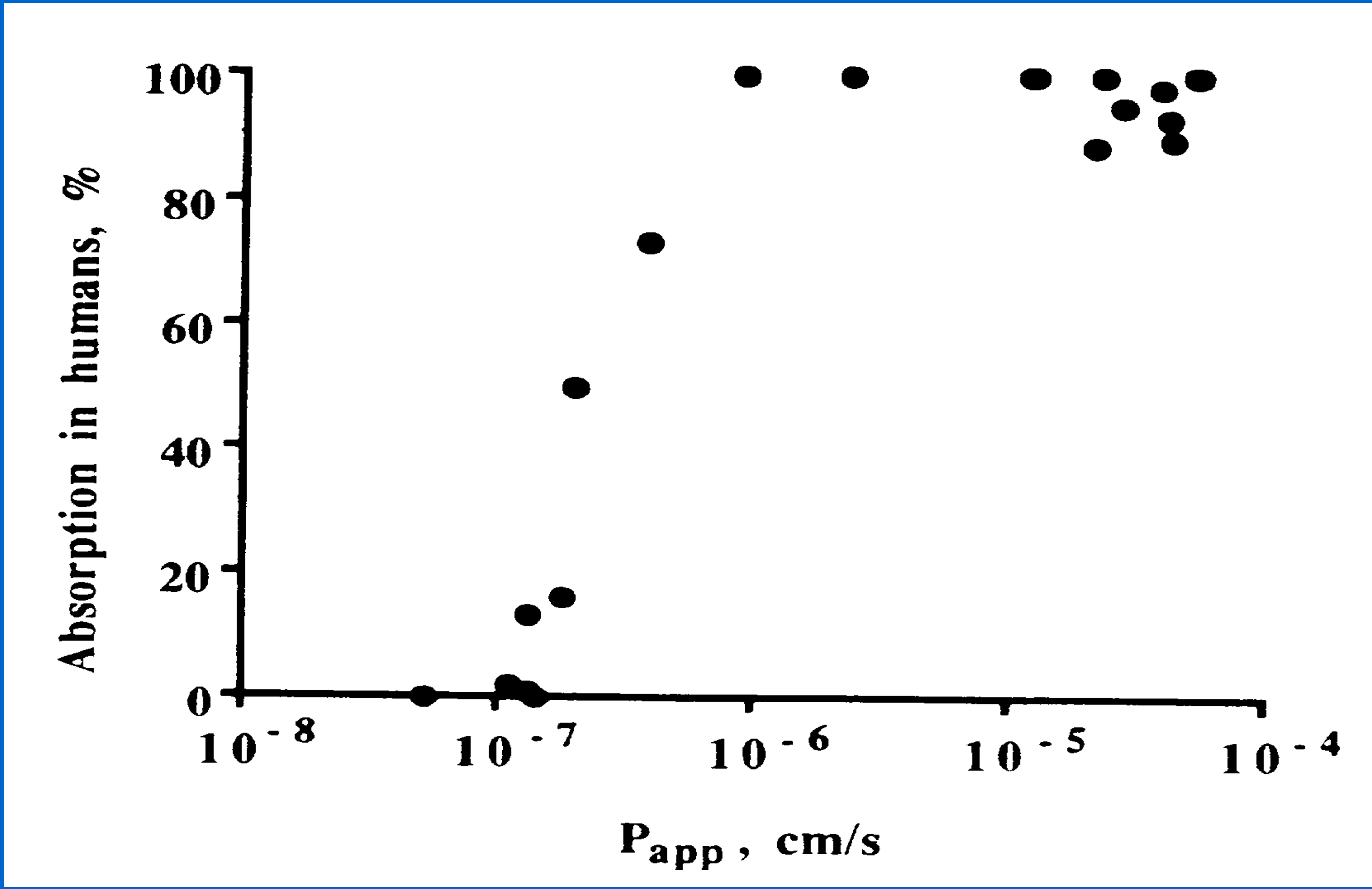
- **Drug Solubility *Relative* to Dose**
- **Dissolution Rate of Formulation**
- ***INTESTINAL PERMEABILITY* of Drug**

# Bioavailability vs. *Jejeunal Permeability**




* From Amidon GL et al. Pharm Res 1995;12:413-20.

# Bioavailability vs. *Caco-2 Cell Permeability* $P_{app}$*




* From Arturson P, Karlsson J. Biochem Biophys Res Commun 1991;175:880-5.

# Evaluation of Caco-2 Cell Model

- **ADVANTAGES**
  - *In Vitro* Method
  - Suitable for High-Throughput
- **DISADVANTAGES**
  - ↓ Paracellular Permeability
  - ↓ Drug Metabolizing Enzymes and Transporters
  - No Hepatic First-Pass Metabolism

# BIOPHARMACEUTIC DRUG CLASSIFICATION *

**CLASS I:**

**HIGH SOLUBILITY-HIGH PERMEABILITY**

- ***in vitro – in vivo*** **correlation generally good**
- ***but*** **no way to account for 1st pass metabolism**

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

# BIOPHARMACEUTIC DRUG CLASSIFICATION *

## CLASS II:

## LOW SOLUBILITY-HIGH PERMEABILITY

- rate of absorption limited by dissolution rate
- *in vitro – in vivo* correlation tenuous since many factors may affect dissolution

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

# BIOPHARMACEUTIC DRUG CLASSIFICATION *

## CLASS III:

### HIGH SOLUBILITY-LOW PERMEABILITY

- Intestinal reserve length is marginal.
- If dissolution is rapid, bioavailability will reflect intestinal permeability and transit time.

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

# BIOPHARMACEUTIC DRUG CLASSIFICATION *

## CLASS IV:

## LOW SOLUBILITY-LOW PERMEABILITY

- *in vitro – in vivo* correlation poor
- good bioavailability not expected

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

# THE BOTTOM LINE

*CLASS I DRUGS:*

HIGH SOLUBILITY-HIGH PERMEABILITY

- *Preferred* as development candidates
- FDA may *waive* repeat *in vivo* testing if initial formulation has good bioavailability*.

* Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, CDER Guidance for Industry, August 2000.